DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

Tuesday, October 22, 2001

8:08 a.m.

Walker/Whetstone Room
Gaithersburg Holiday Inn
2 Montgomery Avenue
Gaithersburg, Maryland

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. LASKEY: Well, good morning. My name is Warren Laskey. I'd like to welcome you all to today's Circulatory System Panel Meeting discussing the premarket application for the Cypher Sirolimus-Eluting Coronary Stent System, P020026. And before we begin, I'd like to thank everyone for their indulgence this morning. Due to some horrific events in our area, a number of us were delayed getting here, so we'd like to thank everyone for their forbearance.

I'd like to ask the Executive Secretary to now read the conflict of interest statement.

Conflict of Interest Statement

MS. WOOD: Before I read the conflict of interest statement, I just have a couple of general announcements.

First of all, Dr. Warren Laskey will be our acting Chair for the meeting today. And I'd like to remind everyone to please make sure that you sign in at the registration desk and also please turn your cell phones off when you're in the meeting.

The microphones that we're using today

require that you keep the button depressed while speaking, so I'd like to mention that for the panel and the speakers' benefit.

The following announcement addresses conflict of interest issue associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. The agency has determined, however, that the participation of certain members and consultants the need for whose services outweighs the potential conflict of interest involved is in the best interest of the government. Therefore, waivers have been granted for Drs. Thomas Ferguson, L. Henry Edmunds, and Mitchell Krucoff for their interests in a firm that could be affected by the panel's recommendations. The waivers involved grants to their institutions for the sponsor's product study in which they had no involvement and for which funding was less than

$100,000 per year.

Additionally, Dr. Edmunds' waiver involved stock in a firm with an interest in the sponsor's product. The stock value is between $25,001 and $50,000. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration other matters regarding Drs. Ferguson, Cantilena, and Krucoff. Each of these panelists reported interests in firms at issue but in matters that are not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions.

The agency also would like to note that, due to the regulations governing covered relationships, the panel Chair, Dr. Cynthia Tracy, will not participate in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him- or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. LASKEY: Thank you. I'd like to now ask the panel members to introduce themselves, starting to my right.

DR. ZUCKERMAN: Bram Zuckerman, Director, Division of Cardiovascular Devices, Food and Drug Administration.

DR. EDMUNDS: I'm Hank Edmunds, University of Pennsylvania, surgeon.

DR. WHITE: Chris White, Ochsner Clinic in New Orleans, Interventional Cardiology.

DR. CANTILENA: Yes, I'm Lou Cantilena, head of Clinical Pharmacology at the Uniformed Services University.

DR. FERGUSON: Tom Ferguson, Washington University St. Louis, cardiac surgery.

DR. KRUCOFF: Mitch Krucoff, Duke University, interventional cardiology.

DR. LASKEY: Warren Laskey. I'm an interventional cardiologist at the National Naval Medical Center in Bethesda.

MS. WOOD: Geretta Wood, Executive Secretary, Division of Cardiovascular Devices.

DR. AZIZ: Salim Aziz, adult cardiac surgeon and clinical associate professor, University of Colorado, Denver.

DR. PINA: Ileana Pina, Heart Failure Transplant, Case Western Reserve University in Cleveland.

DR. BAILEY: Kent Bailey. I'm a biostatistician at Mayo Clinic.

MR. MORTON: Michael Morton. I'm the industry representative. I'm with Soren Cove (ph) Cardiovascular.

MR. DACEY: Robert Dacey, consumer representative from Boulder County, Colorado.

DR. LASKEY: Geretta, could you now please read the voting status statement?

MS. WOOD: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for this meeting on October 22, 2002: Christopher J. White, M.D., Kent R. Bailey, Ph.D., L. Henry Edmunds, Jr., M.D., Mitchell W. Krucoff, M.D.; Thomas B. Ferguson, M.D.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This was signed by David W. Feigal, Jr., M.D., M.P.H., Director, Center for Devices and Radiological Health, on October 10, 2002.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended August 18, 1999, I appoint the following individuals as voting members of the Circulatory System Devices Panel for the meeting on October 22, 2002: Ileana L. Pina, M.D., Louis R. Cantilena, Jr., M.D. Ph.D.

For the record, Dr. Pina is a consultant to the Cardiovascular and Renal Drugs Advisory Committee, and Dr. Cantilena is chairman of the Non-Prescription Drugs Advisory Committee of the Center for Drug Evaluation and Research. They are special government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

Signed by William K. Hubbard, Senior Associate Commissioner for Policy, Planning, and Legislation, dated October 18, 2002.

DR. LASKEY: Thank you.

Introductions

The next segment of our panel meeting this morning is the open public hearing, and I'd like to solicit comments from members of the audience who wish to address the panel. Are there any?

[No response.]

DR. LASKEY: If not, we'll close the open public hearing and begin with the sponsor's presentation.

x [Pause.] 16

Sponser Presentation: Cordis Corporation

DR. LASKEY: I'm just glad you didn't bring a Macintosh with you this morning.

[Laughter.]

DR. DONOHOE: I'll get started while we're looking for the overhead light. Good morning, Mr. Chairman, panel members, FDA representatives, and panel consultants. My name is Dennis Donohoe. I'm the Vice President of Therapeutics and Clinical

Research at Cordis, and I'd like to on behalf of Cordis thank the FDA and the panel for the opportunity to present to you today an overview of the clinical data submitted in support of the Cypher Sirolimus-Eluting Stent PMA.

During the hour-and-15-minute presentation we have, I would like to review some of the background information on this project as well as describe the device, and then spend most of the presentation focusing on the clinical data submitted, particularly the two double-blind, randomized trials, the RAVEL and SIRIUS studies, which provide the primary clinical safety and efficacy data.

The remaining half an hour, Dr. Kuntz will present a variety of subanalyses conducted on the SIRIUS study, then more directly address items that the FDA will be presenting to the panel.

In terms of the background of this project, the FDA granted expedited review of this device given that it offered potentially significant therapeutic advance in the interventional treatment of patients with coronary artery disease. While it is a drug-device combination, the FDA is regulating this as a device given that its primary mode of action is that of a device, that is, the stent, and Sirolimus is simply augmenting the performance of the stent. The PMA was submitted June 28th of this year, and I'd like to take this opportunity to acknowledge and thank the FDA for their rapid responses and clearly expedited review that allows us to come before this panel just four months after the PMA submission.

We believe the clinical data submitted in the PMA and that we're about to review does show the comparability of the safety profile of the Sirolimus-eluting stent to that of the bare stent, that the superiority in terms of all angiographic and clinical endpoints is clearly demonstrated in the data, and that the one- and two-year clinical and angiographic data submitted also demonstrate the durability of treatment over that period of time.

So what is the significance or impact of restenosis following coronary intervention? While restenosis has been long identified as the major limitation for percutaneous coronary intervention, there are approximately one million patients treated in the U.S. per year through some type of intervention of which about 80 percent have at least one stent placed. While both angioplasty and stenting have offered a benefit to these patients, both still carry a restenosis rate. For angioplasty, this rate is variably reported between 30 and 50 percent. Stents have improved this, on average, by about 40 percent but still report a rate between 15 and 35 percent, depending on the complexity of the patient population and the lesion being treated.

This means that on a yearly basis approximately 250,000 patients are returning with restenosis, which means that patients are coming back with recurring symptoms requiring further treatment, either by repeat intervention, repeat angioplasty, stent placement, or brachytherapy, or potentially for surgical intervention.

In understanding the concept of using a drug-eluting stent to try and reduce the restenosis rate, it would help to understand the mechanisms involved in producing the restenosis. This first picture here depicts an artery immediately after balloon expansion, after angioplasty. And as you can see, the plaque has been fully compressed against the internal wall of the vessel. The lumen is fully patent with maximum flow.

Shortly after the procedure is completed, two mechanisms start to take effect that start to contribute to restenosis, the first of which is elastic recoil, and within a matter of minutes to hours after the procedure, the natural tendency of the tissue in the vessel wall causes the vessel to contract down in size. While it is not producing tissue that limits flow within the lumen of the vessel, there is a decrease in the overall lumen side, again, limiting flow.

The second mechanism that contributes to restenosis is that of negative arterial remodeling. This occurs over weeks to several months, and this is basically the healing process following angioplasty in which there is contraction of the vessel over time, again, causing a decrease in the lumen and decreased flow.

These two mechanisms account for the majority of the restenosis that occurs with balloon angioplasty. However, neither mechanism really contributes significantly when restenosis occurs following stent placement. This is because the stent is initially placed, it resists the elastic recoil of the vessel, and also resists the negative remodeling over time.

However, there is a third component that primarily contributes to restenosis following stent placement and is estimated to account for about 30 percent of the restenosis following angioplasty. This is neointimal hyperplasia. This is the result of smooth muscle cell replication that occurs along the internal lining of the vessel wall, allowing cells to increase in volume and migrate into the lumen. As you see, this results in further lumen narrowing and restriction of flow. I think this demonstrates why the basic regulation of this drug-eluting stent is that of a device since the basic function is that of the stent, and that the role of a drug-eluting stent is specifically to target smooth muscle cell replication and prevent that form of restenosis.

I'd like to briefly review the components of a drug-eluting stent system. For the Sirolimus-eluting stent, there is a stent and delivery system, obviously. The stent, as we just discussed, addresses the initial negative remodeling and recoil. The polymer is coated over the metal stent and provides a reservoir for the drug and also provides a consistent release profile for the drug; and, finally, the drug component itself which, as we previously mentioned, is specifically there to inhibit smooth muscle cell replication and neointimal hyperplasia.

The Cypher Sirolimus-eluting stent uses the Bx Velocity stent as the stent platform. This is a balloon-expandable, stainless steel stent. It has been approved in the U.S. for a threatened abrupt closure indication since May of 2000. Stent sizes that are 2.25 to 4.0 millimeters in diameter and lengths 8 to 33 have been approved for this indication. An indication for elective stenting was received in February of 2001. Stent sizes approved for this indication were 3.0 to 5 millimeters in diameter and 8 to 33 millimeter lengths.

There is a volume of data from multiple studies conducted involving this stent, and it is clear the data supports that this stent very adequately addresses the initial negative remodeling and recoil.

The polymer on this stent is composed of two co-polymers that are nonerodable. While the details of this composition will not be presented in this public forum, details are provided in the panel packet.

Each polymer component, in fact, is commercially available in other implantable devices, primarily in the orthopedic area. As I mentioned, the purpose of the polymer is to serve as a reservoir and a control release system for the Sirolimus drug release, and through a variety of in vitro and in vivo testing, the polymers have been shown to be biocompatible, non-thrombogenic, and non-cytotoxic.

The polymer also has inherent elastomeric properties that allows it to accommodate for stent expansion while still serving its primary function of holding the drug and controlling the release profile.

The drug itself, Sirolimus, is commercially available in the U.S. and several other countries on a worldwide basis under the trade name Rapamune, and it is produced and marketed by Wyeth. This drug was approved by the FDA in September of '99 and by the European Community in March of 2001 for chronic systemic use as prophylaxis for renal transplant rejection. The safety and efficacy was established based on two randomized, multi-center studies involving just under 1,300 patients, and it was clearly demonstrated that in order to obtain systemic immunosuppression, chronic administration of between 2 and 5 milligrams per day with the intent of producing a mean whole blood trough level of between 7 and 14 nanograms per ml was required.

Peak blood levels of greater than 200 nanograms per ml following a single intravenous administration have been found to be safe and well tolerated by patients. And Wyeth is supplying Sirolimus to Cordis and has also provided access to the NDA safety data.

To understand the potential value of Sirolimus in inhibiting restenosis, we need to look at the mechanism of action of Sirolimus. Depicted here is representing a smooth muscle cell, and as you see, there are a variety of cytokines growth factors that impinge upon this cell after stent placement that trigger cell replication, and as I mentioned, the main contributor to restenosis is smooth muscle cell replication.

Sirolimus has a specific mechanism of action that blocks smooth muscle cell replication, therefore, potentially decreasing the extent of neointimal hyperplasia. It additionally has some upstream effects and benefits and decreases restenosis by inhibiting some of the inflammation that occurs following stent placement, therefore, decreasing the number of stimulants that cause smooth muscle cell replication.

It inhibits smooth muscle cell replication specifically by binding to a cytoplasmic protein kinase called TOR, or target of rapamycin, and this protein is the main signal that triggers cell replication. Once Sirolimus binds to this protein, it is not activated or able to trigger DNA synthesis, and the cell remains in late G-1. Once Sirolimus is gone, if the stimulants are still present, the cell will be triggered on to move through DNA synthesis and replication. However, if these factors are gone, the cell resets to G-0.

This is a photomicrograph of a Sirolimus-eluting stent. As you can see, all aspects of the metal are fully covered by the polymer containing the drug. There is no exposed bare metal on the stent. In developing a drug-eluting stent, we understand there are two key issues that need to be addressed: the first is what is the effective dose, and the second is what is the period of time that the drug needs to be present to maximize the effect of neointimal hyperplasia.

We conducted a variety of preclinical studies, two of which are presented here. On the left is a rabbit ileac arterial model and on the right is the porcine coronary artery model. In these studies, we used a bare stent and a pure polymer-coated stent with no drug as controls. As you see, there was no inhibition of intimal hyperplasia, but over a variety of doses that were tested, varying the amount of Sirolimus, what we have found through a variety of preclinical studies that consistently a dose of 180 micrograms per stent suppressed neointimal hyperplasia.

Now, to clarify this, as you see at the bottom of the slide, the 180 micrograms refers to the amount of Sirolimus on a 3.5 millimeter by 18 millimeter stent. This equates into 140 micrograms per centimeter square surface area of the stent. So while smaller or larger stents will contain less or more total Sirolimus content, what remains constant is the 140 micrograms per centimeter square.

As I mentioned, the second component we needed to evaluate was the duration of drug release, and we did this by developing two release profiles. Represented in this cartoon to the left is the stent itself, and the lavender area is the polymer-drug combination that is coated around the stent strut. This is a fixed amount of polymer and drug. In some of the stents, however, we put a pure polymer top coat. This served as a diffusion barrier to limit the diffusion of Sirolimus into the surrounding tissue. The result of this is presented in the graph to the right, and this is data from a porcine coronary model in which the fast release--that is, the version that does not contain the top coat of polymer--is represented in the lavender. As you can see, about 95 percent of the drug is released over 14 days. The green is the slow release, which does have the pure polymer top coat. And as you see, approximately 80 percent of the drug is released in 28 days.

Having chosen the preferred dose from the preclinical testing and developed two release profiles, we then moved into Phase I clinical studies. The two Phase I studies that I'll review is the FIM, or First-in-Man, study involving a total of 45 patients enrolled at two centers, and as I mentioned, we tested both release formulations. The second Phase I study is a pharmacokinetic study specifically looking at the release profile for the slow release formulation.

The First-in-Man study involved the enrollment of 45 patients in the treatment of single native coronary artery lesions. The stents used were 3 to 3.5 millimeters in diameter, and all lesions had to be treated with a single 18 millimeter stent. Patients were treated with two months of antiplatelet therapy plus indefinite use of aspirin.

In this study there were two centers. The center in Brazil enrolled 15 patients in the slow-release group and 15 in the fast, while the center in Rotterdam enrolled 15 patients in the slow release. As shown, we conducted angiographic IVUS and clinical assessments at all time points on these patients. In Brazil, the assessments were done at 4 months, 12, and 24, while in Rotterdam, the assessments were done at 6, 18 months, and 24 months.

Before presenting the angiographic data, I wanted to specifically define two terms that were used not only in this study but all clinical data that I'll be presenting--that is, the in-stent and in-segment analyses. As depicted in this representation here, the in-stent analysis includes all measurements that are within the bounds of the stent. The in-segment analysis includes measurements within the stent, but also includes 5 millimeters proximal and distal to the stent.

With that, let's look at one of the angiographic parameters from the study. This is the in-segment minimal lumen diameter. What this represents is the area of smallest diameter over the total in-segment or lesion treated. The left axis is in millimeters and the Y--and the X axis is time and Y is in millimeters. As you see, at baseline and post-procedure the groups are comparable. Green is representing the slow release and lavender is the fast release.

This slide also demonstrates that over the 4- to 12-month period of follow-up there is some decrease in the minimal lumen diameter for both treatment groups, but then after 12 months you see that the follow-up is relatively flat for the period out to 24 months.

This indicates several items: first, that the presence of the drug for the first 4 to 6 weeks does have a suppression of overall neointimal hyperplasia. For a bare stent, this decrease in this 4- to 12-month period would be expected to be in the range of 0.5 to 0.7 millimeters. It also shows that this effect is maintained out through a 24-hour period with only a minimal decrease from the post-procedure, a one-tenth of a millimeter decrease for the slow release, and three-tenths for the fast release compared to the post-procedure MLD.

There were no significant differences in this parameter or any other angiographic parameters in this study between the slow and fast release.

As I mentioned, there was IVUS assessment also done. Multiple methods were used to measure the extent of neointimal hyperplasia. What is represented here is one of those variables, percent volume obstruction. This is a measurement of the amount of luminal volume that is lost over time secondary to neointimal hyperplasia.

As you see, at the 12-month time period there was an impressively small amount of luminal loss or volume loss, only 2 percent on average. At the 24-month time period, there was some additional loss, but really minor compared to the 12-month interval, moving from 2 percent on average to 7 percent. These data again confirm what we saw on the angiographic parameters, that there is sustained benefit over a 24-month period, and, again, if you were to look at what would be expected for a bare stent, this luminal loss at 12 months should be around 25 to 30 percent.

Now, looking at the clinical events in this study, I'd like to again define some terms that will be applied to this study and all other clinical data that I'll be presenting. Target vessel failure was defined as target vessel revascularization with myocardial infarction or cardiac death that cannot be clearly attributed to the vessel other than the target vessel. Myocardial infarction was assessed, both Q-wave and non-Q-wave MIs using the WHO definition, and MACE events were also assessed, that is, major adverse cardiac events, consisting of death, MI, emergent bypass surgery, or repeat target lesion revascularization.

I should indicate, too, that all clinical events in all these studies have been adjudicated by an independent clinical events committee.

This slide summarizes the MACE events at the 24-month time period on all patients enrolled in the First-in-Man study. As you see, there was one death, which I will address in more detail shortly. There were two MIs, three TLRs, one patient accounting for one MI and TLR, with an overall MACE rate that's relatively low for a 2-year follow-up of 11.1 percent. Again, there were no significant differences in any of the clinical events between fast- and slow-release formulations.

The one death that occurred involved a patient who had an initially successful procedure; however, the evening of the procedure they were noted to have change in neurologic status. A CT was performed indicating the presence of an intracerebral bleed, and the patient expired three days later. This event was considered unrelated to the use of the Sirolimus-eluting stent.

The PK study is the second Phase I study. Based on the First-in-Man, which, as you saw, did not demonstrate any differences, angiographic, IVUS, or clinical, between fast and slow release, we chose to develop the slow-release formulation based on the concept that the longer residing time of the drug in the area to be treated potentially would provide more benefit as more complicated patient subgroups were tested.

For this reason, we evaluated the pharmacokinetics of the slow-release stent. This involved two centers, a total of 19 patients, 10 of whom received a single 18 millimeter stent, and 9 received two 18 millimeter stents. Diameters provided were 2.5, 3.0, and 3.5, and as you see here, the doses or total drug content on these stents are listed. The 2.5 and 3.0 diameters contained essentially the same total drug content, 150 micrograms. The 3.5 contains a dose closer to 180 micrograms.

Blood samples were collected starting 10 minutes post-stent implantation and through variable time periods out through seven days. This slide summarizes these data. On the Y axis is the whole blood concentration of Sirolimus in nanograms per ml; the X axis is total number of hours at each sampling time out through the seven-day period. The lavender curve represents the patients who received two 18 millimeter stents, and the green a single 18 millimeter stent.

As you see, the Cmax's are proportional, roughly 1.1 for two stents and about a little bit less than 0.6 nanograms per ml for a single stent. Tmax was the same for both, roughly 3.5 hours. You can see there is a rapid fall-off in the drug concentration over the following 72 hours, with a slower fall-off and a lower drug concentration being maintained because of the slower-release profile of the stent.

To put this in perspective, with the Rapamune dosing these bottom curves represent the data I just presented to you. These two lines represent the therapeutic areas that I mentioned that are needed to obtain systemic immunosuppression.

As you can see, even at Cmax, the total blood level of Sirolimus is ten-fold less than that that is achieved with oral dosing with Rapamune, and at seven days there's more than a 50-fold difference in drug dose.

This indicates that there is a wide therapeutic window between the doses we are using and that needed for systemic therapy. And as I previously mentioned, doses up to 200 nanograms have been tested with no safety issues.

I'd like now to move into the Phase II and Phase III clinical studies. The Phase II study is a RAVEL trial. This was a double-blind, prospective, randomized study conducted across 19 centers in Europe and Latin America. A total of 238 patients were enrolled. And the U.S. pivotal study, the SIRIUS trial, this again was a double-blind, prospective, randomized study in which 53 centers participated, enrolling a total of 1,101 patients.

Let's first look at the RAVEL data. This study involved the treatment of single de novo native coronary lesions. Stents provided were 2.5, 3.0, and 3.5 millimeter diameters, and all lesions had to be treated with a single 18 millimeter stent. There were 120 patients in the active group and 118 in the control. There was good angiographic follow-up at 6 months, 92 percent, and clinical follow-up out through 12 months was 92 percent.

The primary endpoint for this study was angiographic late loss at 6 months; secondary endpoints consisted of an IVUS assessment in a subgroup of patients at 6 months, as well as clinical assessments at 6, 12, and annually out through five years. Antiplatelet therapy for this study involved two months of antiplatelet therapy with indefinite use of aspirin.

As you see here, looking at some of the

key baseline patient demographics, these groups were comparable on all variables tested. There were no significant differences. On average, there were about 18 percent of patients who were diabetic in this study.

This slide summarizes some of the key baseline angiographic results. Again, the average RVD was comparable between these two groups, roughly 2.6 millimeters. All pre- and post-angiographic measurements were comparable, and the average lesion length for these two groups were identical at 9.6 millimeters.

This slide summarizes the lesion, device, and procedural success. What's important in looking at this is to know that the ability to deliver the stent successfully, the Sirolimus-eluting stent, is equal to that of delivering a bare metal stent. And as you can see, the success rate in all three parameters was high for both stents and comparable. There were no significant differences at all between the delivery success of these two stents.

We'll now look at the 6-month QCA evaluation. This slide is summarizing the late loss. Late loss, in fact, is calculated by looking at the post-MLD and subtracting the follow-up MLD. It's an indirect assessment again of the extent of neointimal hyperplasia. And I'm presenting both the in-stent and in-segment results.

As you can see, there was a highly statistically significant difference in favor of the Sirolimus treatment group for both parameters, with essentially zero late loss in the active group and 0.8 millimeters late loss in the control group for the in-stent assessment. And the in-segment, there was a 0.05 millimeter late loss in the in-segment compared to 0.75.

While this term "in-segment" I previously defined, I wanted to highlight that the analysis for the RAVEL study, in fact, went beyond the 5 millimeter boundaries and included measurement of the vessel from side branch to side branch, proximal and distal to the stent.

This is summarizing the binary restenosis rate. This is the percent of patients who have greater than 50 percent restenosis or stenosis at follow-up. Again, these results are similar to the late loss, both highly statistically significant in favor of the active group. There were on patients with binary restenosis in the Sirolimus group compared to 26.6 in the control. In the in-segment analysis, there was one patient for a rate of 0.8 percent compared to 27.5 percent in the control.

As I mentioned, there was an IVUS subgroup analysis at 6 months. The sample sizes are listed here: 69 patients in the active and 70 in the control. You'll note that the external elastic membrane volume, which measures the overall size of the vessel, was comparable between the two treatment groups, as was the stent volume.

All other parameters assessing the extent of the neointimal hyperplasia, again, was significantly in favor of the active treatment group. The neointimal volume was just 2 cubic millimeters compared to 34 in the control group. The lumen volume was larger in the active group at 130 cubic millimeters compared to 103 in the control. And most notably, the percent volume obstruction again was just 1.1 percent compared to 26.1 in the control group--all significantly different in favor of the active treatment group.

We'll now look at the clinical events. This is summarizing the in-hospital MACE events. As you'll note, there were no deaths in either group. There was an equivalent number of myocardial infarctions, and the overall target vessel failure and MACE rates were identical at 2.5 percent for both groups.

This slide summarizes the cumulative MACE events from the index procedure out through the full 365-day follow-up. You'll note there were two deaths in each treatment group. There were no differences, significant differences in the myocardial infarction rate, with 4 in the active and 6 in the control.

There was a target lesion revascularization rate that was significantly improved for the active treatment group, with 0.8 percent in the Sirolimus-eluting group compared to 36.6 in the control. Target vessel failure was also significantly improved in the active group at a rate of 4.2 percent compared to 19.5. And looking at all MACE, again, was significantly in favor of the active group, a rate of 5.8 compared to 18.6 in the control group.

These data are represented here in a Kaplan-Meier estimate of event-free survival, that is, the percent of patients followed through this 360-day period that were free of any of these events. As you see, the 360-day period, there were

94.1 percent of the active group who were free of any of these events compared to 81.2 in the control. This again was significant at 0.002.

I wanted to highlight the two deaths that occurred in the Sirolimus treatment group. They're listed here. First is a patient that expired 330 days post-procedure secondary to a gastrointestinal cancer, and the second patient expired approximately 333 days post-procedure secondary to rupture of a cerebral aneurysm. Neither event was considered related to the drug.

Let's focus now on the pivotal study, the SIRIUS trial. This, as I mentioned, is a double-blind, randomized study. A total of 1,101 patients were enrolled. Patients with single de novo coronary lesions were treated. Diameters for this study that were provided were 2.5, 3.0, and 3.5 millimeter stents. Lesion lengths were to be between 15 and 33 millimeters.

On randomization, you see there were 556 in the active and 545 patients in the control. The primary endpoint of this study, which was agreed upon prior to the initiation of the study by the FDA, was target vessel failure as previously defined. Additionally, there was an angiographic subgroup analysis of 850 patients at an 8-month assessment point, and there was an IVUS subgroup involving 250 patients, again, with an assessment at 8 months.

Antiplatelet therapy was provided for 90 days in this study with indefinite use of aspirin. I should say also that angiographic and IVUS analyses were conducted by an independent core lab.

Following the randomization, there were a total of 43 patients that were deregistered. The statistical section of the protocol identified the primary analysis as that of intent to treat. The intent-to-treat population was defined in the protocol at those patients who at least had an attempt to use the study device. In this study, there were 43 patients who, in retrospect, were prematurely randomized, after randomization were found not to qualify for the study, and I'll give you some more detail on these. There were 23 in the active and 20 in the control group, leaving us with an analyzable group or an intent-to-treat group of 533 patients in the active, 525 in the control.

As I mentioned, there was 8-month angiographic follow-up and 9-month clinical. There was a high angiographic follow-up rate of approximately 85 percent of the patients, and approximately 96 percent of the patients with clinical follow-up out to 9 months.

This slide summarizes the reasons why these patients were deregistered. There were two patients in each group who, after randomization, were found not to have the stent size available needed to treat their lesions. The bulk of the deregistered patients were, in fact, patients who were randomized and then found not to actually qualify based on the inclusion/exclusion criteria of the protocol. There was one patient in the control group who withdrew consent following randomization, and that gives us the total of the 43 patients.

This slide summarizes the patient demographics at baseline. The intent of the SIRIUS trial was purposely to challenge this drug-eluting stent and to provide data from what was considered more of a real-world patient population. We think the study has done that, and approximately 30 percent of the patients had prior MIs, with about 24 percent having prior revascularization and about 26 percent with diabetes. There were no significant differences in any of the patient demographic variables.

This slide summarizes some of the key lesion characteristics. Again, you'll note the standard 44 percent with LEDs, and there were a total of about 55 percent of patients who had Type B-2 and C lesions. Again, these are lesions with more diffuse disease, more calcium and plaque buildup, and more tortuous type vessels.

There was also a provision for allowing for overlapping stents, and as you see, there was an average of about 27 percent of patients between the two groups that did use overlapping stents in the study. There were no significant differences in any of these variables.

This slide summarizes the baseline angiographic results. Again, you'll note the groups are comparable. There are no significant differences in any pre- or post-evaluations. The post--or pre-procedure RVD was equivalent between the two groups with an average of 2.79 millimeters, and the average lesion length was identical at 14.4 millimeters.

Again, we're summarizing the key success measurements from the index procedure, and, again, you'll note that there was equal performance with no significant difference between the Sirolimus-eluting stent and the bare metal stent.

Let's again look at the late loss. This time in the SIRIUS trial, it was an 8-month QCA assessment, and, again, I'm presenting in-stent and in-segment. Again, you'll see, as we did in RAVEL, a highly significant difference in favor of the active treatment group, with a late loss in-stent of just 0.17 millimeters compared to 1.0 millimeters in the control. The in-segment analysis showed a late loss in the active group of 0.24 millimeters compared to 0.81 millimeters in the control group.

And the restenosis rates, again, replicate what we see for the late loss, both assessments significantly in favor of the active group, with only 3.2 percent of the patients in the active group having in-stent binary restenosis compared to 35.4 in the control group. The in-segment analysis, we see 8.9 percent of the active patients with binary restenosis compared to 36.3 in the control group.

The IVUS subanalysis presented here, as you see, there are 99 patients in the active and 76 in the control. There was no difference in the EEM volume or stent volume between these two treatment groups, and in all IVUS variables for neointimal hyperplasia, they were all highly significantly different in favor of the active treatment group.

Just to highlight two of these, again, the neointimal volume was just 4.1 cubic millimeters at the 8-month follow-up for the active group compared to almost 57 cubic millimeters in the control group. The percent volume obstruction, as we've seen in First-in-Man and RAVEL is relatively constant at about 2.6 percent compared to 34.2 in the control group.

We'll now look at the clinical events, and this slide summarizes the in-hospital events. There was one death in the active group. There were no significant differences in the MI rate, nor were there any differences TLR, TVR. In fact, the MACE rates and TVF rates were comparable with 2.4 in the active group compared to 1.5 in the control group.

Now, if anyone--I believe somebody shut the power off to this plug here, if someone could turn that back on.

We're going to look at the clinical events from out of hospital through the 9-month follow-up. As you see, there were four deaths in the active group compared to three in the control. There were no significant differences. The overall MI rate was marginally significantly different in favor of the active treatment group, and this was driven by the significant difference of non-Q MI rates with one patient, or 0.2 percent, in the active compared to 1.3 in the control. There was also a significant difference in TLR, MACE, and TVF in favor of the active treatment group. TVF, there were only 6.4 percent of the patients with target vessel failure compared to 19.6 in the control group.

This next slide summarizes all clinical events from the index procedure out through nine months, and in this slide we will present specifically the primary endpoint of the study, which included all MACE events, all events, target vessel events, from the index procedure through the full nine months. As you'll note, there were no differences between the death rates. There were five in the active and three in the control, and I'll provide more data on these five patients. There were no significant differences in MI rates.

However, again, there was a highly significant difference in favor of the active treatment group for clinically driven target lesion revascularization with 4.1 percent compared to 16.6 in the control group. The target vessel revascularization not including target lesion was comparable between the two groups. The MACE events were significantly different, 7.1 compared to 18.9 percent, and the primary endpoint of the study was highly significantly different, again, 8.6 in the active compared to 21 in the control group.

This slide summarizes the five deaths that occurred in the Sirolimus-eluting treatment group. As you see, there was a patient who died of a cerebral hemorrhage following the index procedure. This was adjudicated by an independent committee as a cardiac event simply because it was related to the procedure and potentially to the use of 2b/3a inhibitors. The second patient had multiple organ failure, including pneumonia, liver dysfunction, renal failure, and congestive heart failure. The third patient expired secondary to renal cell carcinoma. The fourth patient had a subdural hematoma following head trauma. And the fifth patient had a stoke and died of acute intracerebral hemorrhage. None of these events were considered related to the use of the Sirolimus-eluting stent.

This curve here, again, represents a Kaplan-Meier estimate of event-free survival for TVF. As you see, there was, again, a significant difference with 91.1 percent of the active group free of target vessel failure compared to 78.6 percent in the control group.

Looking at the same event-free survival, but this time looking at target lesion revascularization specifically, again, we see a significant difference at the 9-month follow-up, with 95.7 percent of the active and 82.9 percent of the control group event-free survival.

The angiographic core lab conducted very detailed angiographic evaluations on these patients. I wanted to specifically highlight for the panel this analysis which specifically looks at not only the in-stent late loss but also the margins, the proximal 5 millimeters and distal 5 millimeters.

As you can see, the late loss in each segment analyzed is significantly decreased in the active treatment group. So this data indicate that there is no evidence for an edge effect or candy wrapper effect in using this stent.

I'd like now to quickly review a variety of safety assessments that were conducted through the RAVEL and SIRIUS trials. The first is the use of overlapping stents. As I indicated, there is on average about 26, 27 percent of patients who had overlapping stent use. The total stent length in this patient population was about 20 millimeters. The in-hospital MACE rates were equivalent. The stent thromboses rates were equivalent, with one SAT in each treatment group. There was one aneurysm in each treatment group, and, most notably, the MACE events and target lesion revascularization rates through 9 months were, again, significantly improved in the active treatment group, with the same relative improvement we saw in the overall patient population.

This slide summarizes the stent thromboses across these two studies. In the RAVEL study, as I mentioned, there was only 60-day antiplatelet therapy provided. There was no thrombosis in either the active or the control group through the full 365-day follow-up.

In the SIRIUS trial, which involved 90 days of antiplatelet therapy, there were two thromboses in the active and four in the control. One each had a subacute thrombosis, and there was one late in the active group and three late thromboses in the control group and, again, no significant difference.

When we looked at aneurysms, there were no aneurysms reported at the six-month angiographic evaluation in RAVEL for either treatment group. There were two aneurysms in the active group found at 8 months in the SIRIUS study and four aneurysms found in the control group. This was not significantly different. You'll note that the rates for the control group was around 1 percent, which is in the range of expected background rate of 1 to 3 percent. No adverse events were associated with any of the aneurysms, and we used a fairly liberal definition for aneurysm of a ratio of 1.2 or greater.

Now, I wanted to review incomplete apposition. I know this is not a new phenomenon. It has been identified before. However, I wanted to review some basic definitions with the panel.

This term "incomplete apposition" also is sometimes referred to as malapposition, and by definition, you'll note at the bottom of the slide, this is defined as a separation of one or more struts from the vessel wall with evidence of blood behind the stent struts. So this is an IVUS evaluation or IVUS definition.

At baseline, it is possible to have incomplete stent apposition if the stent is not fully deployed and fully apposed to the vessel well. This is represented here by the evidence of blood flowing behind the stent struts and the vessel wall separated from the stent.

Over time, there are two options. This may progress to complete healing, that is, a neointimal hyperplasia takes place, this gap is filled in with tissue, and on follow-up the stent appears fully apposed. It may also be preserved or persist over the follow-up period. If no or minimal intimal hyperplasia takes place, the gap will still be present over time.

The other variation on incomplete apposition is defined here. At baseline, you may have full stent apposition to the vessel wall, but on follow-up you find that there is a gap. This is referred to on this slide as late incomplete apposition. Again, there's a gap that appears. And in this model, you'll notice the total vessel area remains the same. It's also possible to have late incomplete apposition with positive remodeling, meaning that the gap, at least in part, is associated with expansion or increased area of the vessel size.

So with those definitions, let's look at some of the data we have on late incomplete apposition. As I mentioned, this is not a new phenomenon. It has been defined with bare stents, and specifically there was an article just published last week in Circulation which specifically looked at bare stent placement and IVUS at baseline and follow-up at 6 months on 206 patients. They found a late incomplete apposition rate of 4.6 percent. They also found that all nine of the patients had some evidence of positive remodeling, and none of the patients had any clinical events through that follow-up time period.

When we look at the RAVEL study, the RAVEL study did not have obviously the baseline. It was only conducted at the 6-month follow-up. So we were not able to differentiate preserve from late. We can only identify those patients who had incomplete apposition at the 6-month follow-up. This is summarized here. There were ten patients in the active group and two patients in the control, which was significantly different.

When these events occurred, we did ask these 10 patients to return for an 18-month clinical angiographic and IVUS assessment. And as you'll note in the box below, nine of these ten patients have returned for evaluation. In all nine patients evaluated, the incomplete apposition has remained. None of the ten patients had any clinical events reported out through the 18-month period, and there are no other angiographic findings except for one patient who was noted to have an aneurysm on follow-up in the same area. This patient was asymptomatic for the aneurysm and was noted on earlier IVUS assessment to actually have evidence of a large hemorrhage within the vessel wall in the area of the aneurysm formation.

In the SIRIUS trial, we did conduct an IVUS evaluation at baseline, post-stent deployment, as well as the 8-month follow-up. You'll see here post-stent deployment there was an equivalent number of incomplete appositions in both groups, 14.3 and 14.9 percent. At the 8-month assessment, there were 18.7 percent of the patients in the active group and 9.2 in the control with incomplete apposition, which was marginally significant, 0.08.

Given that we had baseline and follow-up IVUS, we were able to differentiate and better define where these incomplete appositions came from. When we looked at this in a matched-pair group--that means a group that has a baseline IVUS as well as a follow-up, with automated pull-back--you see there was an equivalent number of patients who had resolved late incomplete apposition, an equivalent number had persistent incomplete apposition.

However, there were nine patients, or seven patients in the active for 9.7 percent and no patients in the control group that had late incomplete apposition. This was significantly different.

When we evaluated these patients in more detail, we found that none of the patients with overlapping stents had late incomplete apposition in the area of the stent overlap, which potentially is the area that would double the drug dose. Additionally, we found that none of these patients experienced any adverse events through this 9-month follow-up period, and three of these patients had evidence of positive remodeling.

So what can we say in conclusion? Well, we know that with bare stents this is seen in the range of about 4 to 5 percent, and, most importantly, in terms of the clinical significance of this is the concern about increase in the stent thrombosis rate because of the exposed metal. As previously shown to you, there is no increased rate of stent thrombosis in the Sirolimus treatment group. In fact, the rates in both studies are less than 1 percent. And this is assessed a period of time after the patients have been off antiplatelet therapy from 6 to 16 months.

As mentioned, the bare metal stents not only in the published reports but other data that's been released recently is reporting a late incomplete apposition rate of 4 to 5 percent. We also know that in the literature, brachytherapy has been associated with late incomplete apposition in the range of 5 to 10 percent. And, typically, these late incomplete appositions have not been linked with an adverse event. We recognize there is an increased rate of late thrombosis with brachytherapy, but this is more related to the issue of complete re-endothelialization.

There is also a model that we can look at from a clinical standpoint on a daily basis. Patients have stents placed across side branches where technically are exposing metal to flow and not compressing tissue, and this in and of itself does not increase the risk of stent thrombosis.

And, finally, as I mentioned, there was no evidence of late incomplete apposition in the area of increased dose, suggesting that it is not a direct drug effect causing this.

The final topic I'd like to review starts to specifically address one of the issues the FDA will present around the question of whether we have sufficient safety data for the full stent lengths and diameters requested. This slide summarizes data from the SIRIUS trial. As you see, on the Y axis this is number of patients, and the X axis is the reference vessel diameter. This study provided 2.5, 3.0, and 3.6 millimeter stents. But as you can see, when you look at the RVDs, 146 patients or roughly 27 percent of the patients involved in this study, in fact, were treated with vessel diameters less than 2.5. On the upper side, again, while the largest diameter stent was 3.5, you see that, in fact, there were 31 patients treated with vessel diameters greater than 3.5.

This slide, again, summarizes the data in the SIRIUS trial, but this time looking at stent length. And while the predominant stent length was in the area of 10 to 20 millimeters, you'll note there were 173 patients or roughly 31 percent of the patients in this study that, in fact, had stents used that were more than 20 millimeters in total length.

To look at this another way and directly address the issue of the amount of safety data we have for drug and polymer, this is taking the same data I just presented to you. In this we're looking at number of patients on the Y. The first parameter on the X axis is the total amount of drug--that is in micrograms--that the patient is exposed to. The second line is representing the total amount of polymer.

As you'll see, while the greatest number of patients were treated with between 150 and 250 micrograms of drug, in fact, there was a group, 20 percent of the patient population, that had drug and polymer exposure greater than 250 micrograms or greater than 700 micrograms.

If we look at the group potentially at highest risk for the highest drug dose and polymer content, their adverse events are listed at the bottom. As you see, there were only two peri-procedural MIs; three TLRs, one of which was peri-procedural; no aneurysms, no thromboses, and one late incomplete apposition. So this does not suggest that there is an increase in adverse events and that there was a broad exposure in terms of the drug and polymer.

Finally, this slide summarizes the drug content matrix. This is the list of stent lengths that Cordis is requesting for approval, and these are the stent diameters. If you look at this matrix in each box, it provides the total drug content by that combination of stent diameter and length. If you roughly triple that number, you'll have the polymer content.

As you can see, based on the data I just showed you, we have a large majority of the data from these studies, including drug exposure up to 350 micrograms, with about 94 percent of the patients included in this shaded area.

With that, I'd like to now turn the presentation over to Dr. Kuntz, who present a variety of subanalyses on the SIRIUS trial.

DR. KUNTZ: Good morning. My name is Rick

Kuntz. I'm an interventional cardiologist at the Brigham and Women's Hospital in Boston. I'm also the chief of the Division of Clinical Biometrics there and the chief scientific officer for Harvard Clinical Research Institute, which ran this trial.

This is my financial disclosure slide. I have no equity or consulting relationship with Johnson & Johnson or Cordis. The Harvard Clinical Research Institute is a nonprofit contract research organization in Harvard who ran this trial. Cordis does provide an educational grant to the Department of Medicine, the Brigham and Women's Hospital for fellowship training in clinical trials, and the travel expenses for today's trip were reimbursed by Cordis.

I have two slides that I think are attached to the back of your section, and this is one of them. That may not be in the right order, and I'll tell you about the other one.

In order to motivate why we do multivariable modeling, I can tell you academically we're interested in looking at mechanisms of how things work. And, in general, the fun part, I think, of analysis is the multivariable modeling after a study.

In a study that's positive overall for the randomized portion, sometimes the subset analysis may disclose a lot of things that you don't want to look at. But, in general, subset analysis is helpful in determining patient subsets that may or may not benefit from a therapy shown to have an overall favorable effect as in this study. But this analysis is often risky since subsets are markedly diminished in their power to demonstrate an overall effect compared with the overall sample for which the trial was powered.

This type of analysis, however, has demonstrated the anti-restenosis benefit of stenting. It's demonstrated the relationship mechanistically between the gain in an artery of a lesion for stenting compared to the loss, the so-called loss index. It's the technique that has been used to demonstrate the impact of diabetes on restenosis, and a lot of other mechanistic issues that we use in regular analysis for percutaneous trials over the last 15 years.

All such analyses have generally been linear, that is, either we look at the linear regression or we look at a general linear model of the loge (?), for example, linear link, and this is typically used for biological systems. So these are conventional kind of boilerplate analyses that are performed.

We know that if we're looking back at the last 15 years of angioplasty and stent trials from over 100 studies and probably over 30 or 40 well-designed clinical randomized trials that there are three major characteristics that affect the outcome of restenosis in studies, and they include reference vessel size, the length of the lesion or the stent that you use to treat that lesion, and the presence of diabetes.

Now, it's important for us to evaluate these because some diseases don't have a lot of influence by case mix issues of the patient population. But restenosis does have a lot of influence due to issues due to the patient, that is, the size of their vessel, the length of the lesion, or the presence or absence of diabetes.

We know that when we analyzed those factors in this study, we saw the same effect--that is, we saw significant relationships of these factors, as we would expect, for the size of the vessel, that is, larger vessels have low restenosis rates; the length of the lesion, that is, longer lesions have higher restenosis rates; and the presence of diabetes, that is, patients with diabetes have higher restenosis rates overall.

It's important that in order to make sure that the randomization worked, that when we adjust for these strong influential factors that we have a treatment assignment outcome which is still significant. So, therefore, what this models tells us is that the overall treatment assignment to Sirolimus was still independently significant in its ability to reduce restenosis, in this case angiographic restenosis measured by narrowing, after adjustment for these powerful predictors of the outcome.

If we look at an orthogonal outcome, that is, clinical restenosis--again, not measuring angiographic narrowing but the need for repeat of revascularization determined clinically--we see the same predictors have the same influence overall, are highly significant, and an independent effect of the overall treatment assignment on the improvement in clinical restenosis, which is quite powerful.

We know from previous studies on accumulated stent databases--and this is from previous stent studies approved by the FDA--that the influence of these three factors--lesion length, the size of the vessel, and the presence or absence of diabetes--have profound effects on the instance of angiographic or clinical restenosis. In this matrix, what I've done is shown the incremental sizes of the vessel, the lengths of the lesions and bends, and the presence of diabetes to develop about 24 different cells here. And one can see that patients that have short lesions and are non-diabetic with small lesions, short lesions in large vessels, generally have low restenosis rates.

On the other hand, the same patients with the same stents who have long lesions and small vessels and are diabetic could have almost a four- to six-fold increase in restenosis rate overall. So this is important to know because when looking at a new therapy that looks positive, like Sirolimus, we want to see that the effect has some kind of uniformity over this wide range of case mix. That is, if we see that there's a six-fold difference in the restenosis rate based on patient variables, we'd like to see that this drug can hold up under those conditions.

If we analyze, in fact, the control arm, the bare stent arm of this study, we see the same relationships exist here as we've seen from previous stent trials. That is, we see the same low rates of restenosis in patients that have no diabetes, large vessels, and short lesions compared to patients with diabetes that have long lesions and small vessels. So we see the same gradient that we see from previous stent trials, and that, in fact, is pretty consistent in this study as well.

If we look clinically at that--that was an angiographic measure, again, a different way of measuring failure--we see the same gradient, low rates of clinical restenosis for large vessels and small lesions in non-diabetics, and high rates of restenosis for long lesions, small vessels in diabetics.

Now, if we look at the outcome of the active arm in this study, the Sirolimus arm, we see the same gradient exists there as well, that is, these main effects still affect those patients assigned to the drug, but the rates are substantially lower in these cells compared to the previous control arm and, hence, the overall mean average was different, as Dr. Donohoe showed earlier. And if we look at this predictor of angiographic restenosis, we have rates that go from as low as 3 to 4 percent in patients with big vessels and short lesions and non-diabetics to as high as 24, 25 percent of patients with diabetes and long lesions, suggesting that we still have issues with patients with diabetes, but hopefully we've substantially lowered this to a good degree as the first start.

Clinically, if we measured that, we can see the numbers. They still have the same gradient but are substantially lower. That is, this is the clinical impact on patients who require repeat revascularization, and one can see that it ranges from about 2 to 3 percent to about 10 percent.

Now, one way to be able to evaluate the impact of the therapy in this randomized trial on those different patient subsets is to subtract out the rates of restenosis from the two matrices, and you can get an absolute reduction estimate. Here we look at an angiographic restenosis outcome, and this is the difference between the control arm and the Sirolimus arm and shows the amount of restenosis episodes that are saved by the Sirolimus arm. And we can see that it's important to evaluate patients at risk.

Patients at the highest risk here, the smallest vessels and longest lesions, had the biggest reduction in restenosis overall, suggestive of the fact that this did work well across low-risk and high-risk patients; and, in fact, patients that benefited the most were the ones with the highest risk.

Another way to evaluate that is to calculate the treatment effect, and that is to basically look at the baseline risk minus the active risk, that is, the control versus active. And this is the relative difference in treatment, and one can see here that the relative difference or treatment effect is relatively uniform over all of these different cells. So this is, I think, quite profound because of a few reasons: number one, we have 18 cells here, different ways of cutting patients up, and we have diabetics, non-diabetics, long and short lesions, small or short vessels, and we have a very uniform treatment effect that goes from 64 to 81 percent across all of these cells.

The other striking thing here is that the treatment effect here--and in this case, angiographic restenosis--is in the 60 to 80 percent range, much higher than what we normally see in contemporary therapies that leads to changes in standard of care, which is on the order of 25 to 35 percent. So not only is there a profound treatment effect in reducing angiographic restenosis here, but it's very consistently demonstrated over a wide variety of characteristics that have tremendous impact on the risk of restenosis.

If we look at the clinical reduction--again, the other way to measure failure is to look at clinical need for repeat revascularization--we see the same distribution of uniform high rates of reduction over a wide range of different risk factors.

Now, there are other ways to demonstrate these subset analyses, and one common way is to illustrate the odds ratios using an odds ratios table. In this slide, it looks a little bit complex. Let me orient you here.

Here we have the odds ratios of 1.0, which is the unity line--that is, those therapies when compared between control and active--if they fall in this line, there's no benefit. If they fall to the right of the line, there would be benefit for the control arm. If they fall to the left of the line, there would be benefit for the active arm.

The overall odds ratio here is approximately 0.2 with a rate of 4.1 percent versus 16.6 percent in the analysis of in-segment restenosis.

If we look at the individual groups broken down by those of interest, like gender, for example, and those that we have predicted previously to be problematic, like diabetics and so on, we see that when we cut the patients into various different groups--male, female, diabetics, non-diabetics, LAD location, non-LAD, small vessel, large vessel, short lesion, long lesion, patients with overlap or no overlap of their stents--there's a very consistent relationship of the estimate of the odds ratio in strong favor of the treatment assignment to Sirolimus with the 95 percent confidence intervals, they're very far from the unit line, suggesting a significant difference, and the significant values are illustrated here by the p values (?) .

Now, if we look at the odds ratios per se in clinical restenosis, we see the same relationship, very powerful odds ratios to the left of the unity line, suggesting a variety of different odds ratio benefits for all the different patient subsets that I illustrated earlier.

Another important metric that you can use looking at odds ratios is the number of events that can be prevented per thousand patients, and one can see here that the number of events preventing clinical restenosis is in the 200 to 300 range in most of these variables. And if you take a thousand divided by that number, that's the next number needed to treat in order to prevent an outcome, and that number average between 4 and 5, which is very low for contemporary therapies. So all these analyses here do suggest that over a wide range of different patient subsets, there's a profound and consistent difference overall.

Now, one thing that's important to also illustrate is that you can actually look for differences in subsets by testing for interactions. That is, we want to know, for example, whether there's interaction between the treatment effect and a patient subset. Did diabetics have the same benefit from the active arm as non-diabetics per se? And you can test that with interactions. We found that there were no interactions except for one, and that existed here in the large and small vessel.

But this is a very interesting interaction. What we see here is that there was a significant difference in the benefit for patients assigned to Sirolimus for large vessels compared to small vessels, but the differences were all significantly better than control. So what we see is that we see two significant benefits, one super-high benefit and one moderately high benefit. So the only interaction we could define here was in the zone of positivity to show significant differences at this level, but still both sides better than unity.

Now, this analysis can be very helpful because when we get to the prescriptive side of understanding why we do multivariable modeling, it's for us to understand how to use stents. For years we have always known that as you put stents in with longer and longer lengths, you're going to have higher and higher restenosis rates per se. And the admonition has always been to try to use as short a stent as possible in order to minimize restenosis. And if we look at the regression between stent length and the restenosis outcome from in-segment restenosis or angiographic outcome, in the control arm we do see this increment in restenosis risk as you add each millimeter of stent per se.

But, as expected, if we applied this to the Sirolimus arm, we see that the same slope exists, but it's a lower slope. That is, we do see a significant increase in increment associated with stents, but the price paid for each increment in millimeters is very tiny compared to the price paid for the bare stent per se. And this is very helpful because often the interventional cardiologist has to wrestle with using a stent that may cover the lesion from the normal part of the artery to the normal part in order to prevent dissections versus trying to stent the obstructive portion of a lesion where they may want to minimize restenosis but trade off the possibility for dissection.

This would suggest that the incremental price paid for using the longer stent is very minimal compared to what we're used to with bare stents.

If we look at that same analysis using clinical restenosis, we see the same slope relationships, that is, an improvement that classical expected outcome of incremental risk associated with clinical restenosis with longer stents and the very shallow relationship seen in offset for those patients assigned to Sirolimus.

So in our conventional subset analysis, the analysis that has been done for many studies in the past and has led to a lot of understanding of mechanistic outcomes, our analysis has demonstrated a consistent and strong treatment effect of Sirolimus across a variety of important subset categories. And there was no treatment interaction demonstrated of a patient subset that did not benefit from Sirolimus from, I think, a rather comprehensive analysis.

Now, there are a lot of ways to do subset analyses, and we've shown you one way, which I think is a rather conventional way. The FDA has performed a variety of subset analyses, too, and I'd like to address those issues now.

The reason to address those issues is because the FDA performed a lesion length and vessel size analysis on the results, which we've shown here, which actually demonstrated a reduced efficacy for Sirolimus.

The FDA analysis relied on a comparison of multiple subsets to demonstrate individually statistical significance. For example, in one of the analyses, each 5 millimeter increment of lesion length was tested for statistical significance.

The FDA applied nonlinear models to the data to demonstrate limited efficacy of Sirolimus. The FDA also suggested that TVF, or target vessel failure, our primary endpoint, should be measured at 7.5 months rather than 9 months as pre-specified. And the FDA suggested that the trial may have been unblinded, and this may have led to higher rates of clinical restenosis in the control arm.

Now, if we look at the notion of measuring lesion length and vessel size to demonstrate reduced efficacy for Sirolimus, our subset analysis was positive. So we weren't able to reproduce the overall effect per se, and I've shown you those cases already. We demonstrate that when we look at lesion length and vessel size, using our conventional methods, we actually demonstrate it has a profound effect that's consistent over all those different subsets that I showed you earlier. So we couldn't reproduce the overall analysis to demonstrate any vessel size reduction in restenosis.

The FDA analysis relied on a comparison of multiple subsets to demonstrate individual statistical significance, and I think there's some bar graphs that demonstrate the overlaps of the confidence intervals. Well, for each 5 millimeter increment of lesion length, you actually reduce power, and so each 5 millimeter subset is actually necessarily underpowered for a comparison in general.

Usually when you compare subsets broken down into bends, the comparison of subsets is done to demonstrate a consistency of the estimates of the results, but not held accountable for each bend to demonstrate statistical significance.

Here's the demonstration of the actual raw data. This is not modeled. This is just the unadjusted outcomes of restenosis, in this case the primary endpoint target vessel failure by lesion length. We can see here that the open circles, if you can see them, are generally all above the black circles here. The open circles are the control arm. The black circles are the Sirolimus arm. And what we can see is that over the range of restenosis rates per se, we opted to use linear modeling because there was a general trend of increasing restenosis with longer lesions, as we'd expect, and a lot flatter slope with the black line dots here, and even at the play of chance, by and large most of these dots are lower in general. So we saw that over the course of the different bends we saw consistent effect overall of reduction in restenosis.

If we look at the categories based on reference vessel size, which was also evaluated by the FDA, we also see a consistent relationship of reduction of restenosis as you get bigger, but the offset was higher--higher event rates for the control arm compared to the assignment to Sirolimus. Again, this would be something we would generally model as linear because of the overall kind of scattergram here, although it looks rather linear per se. So we opted to use linear modeling because it just made more sense, and all the estimates here do, in fact, show, I think, a consistent outcome.

If we look back at the lesion length categories per se, we also saw that in an area that the FDA had tested, we did see a significant effect that was greater for lesions over 20 millimeters. So even when we bend the patients over here alone and necessarily look at this underpowered subset, we still saw significant improvement in restenosis with that subset of greater than 20 millimeters for the primary endpoint, which was 9-month target vessel failure overall. So we didn't see the reduction in effectiveness even when we looked at the subset greater than 20 millimeters per se.

We did look at their analysis on 16 millimeters or greater where we did see a significant reduction, but this was, I think, an issue of play of chance, because if you look at the breakdown of each millimeter, this is often seen in random data sets; that if you break it down, the valuation of greater than this number was highly significant for the Sirolimus arm compared to the one for 16, and the one for 16 was pointed out by the FDA as being the one not significant. But I think that the other ones are all consistent with being a positive result.

The FDA applied nonlinear models to the data to demonstrate limited efficacy for Sirolimus. We could not reproduce the nonlinear quadratic or cubic models, nor could we justify its use by measurements of discrimination or calibration, which are the statistical terms that statisticians use for goodness of fit. Essentially we did a lot of analysis using nonlinear terms, and by our analysis the linear modeling was still the appropriate technique to fit the data.

The FDA suggested that TVF should be compared at 7.5 months in a few of their analyses rather than the conventional 9 months as prespecified. And I'd like to just talk to you about that because it's a very complex issue.

The 9-month TVF endpoint is generally the standard endpoint used for measuring clinical restenosis, and there's a reason why. The prespecified 9-month endpoint requires carefully orchestrated and coordinated timing for the angiographic follow-up cohort. Analysis of these data, which is designed to measure the outcome at 9 months is not intended for analysis prior to 9 months because the orchestration of how you bring patients back for angiography.

This is because previous studies have demonstrated that clinical restenosis is best measured by going out as far as possible. That is, in this study of 2,000 patients in the starter study, we know that if you measure restenosis even up to a year, you still get a better estimate of the restenosis rates than compared to 6 months per se. So, in general, working with the FDA over the years, it's been a standard to adopt the 9-month endpoint because it's a common middle ground between the 6-month angiographic narrowing that we know about and the 1-year clinical. So we picked the 9 months per se. So there's a rationale as to why you use 9 months overall.

And one might think, well, haven't there been studies that demonstrate that narrowing happens at 6 months by all the angiographic studies done in Holland and Japan, and the answer is yes. But the clinical events that we measure are actually the actual revascularization event that occurs. And this is actually frame-shifted to the right by a few months, because after the biological narrowing occurs, the patient develops clinical signs and symptoms. The provider has to become aware. They have to be scheduled for repeat revascularization, which may take in some cases, especially outside the United States, up to several months. And then the patient actually has a revascularization event.

Because of this frame shift from the biological thing, we've also adopted an endpoint which is around 9 months for the outcome.

Now, the FDA has suggested that the trial may have been unblinded and that this may have led to a higher rate of clinical restenosis for the control arm. Let me explain what happened here.

Each site had a stack of A and B blinded stents that were used in the study, one of which was active and one of which was not active. And the notion might be that the potential for investigators could have systematically correlated the blinded Group A versus Group B when they started to see the follow-up that, say, Class A didn't have as much restenosis as Class B, and they would get the notion that Class A might have been the study drug. And that's something that's definitely a potential, and it's true with any study where you try to do blinding under such a classification.

We had basically felt that this might be a problem because that tendency occurs in cases where you actually have positive results, because if you do see that one arm is not coming back with a lot of restenosis, you are vulnerable to being able to have the investigators correlate that, and that happens in a lot of randomized trials.

So by anticipating that, we had set up a blinded CEC, which is typically for studies, that would be the final arbitrator for all the outcomes and would require demonstration of narrowing and clinical investigations to call an event an event. And, of course, this CEC was blinded to the--Clinical Events Committee was blinded to the assignment.

So if we look here, we see that there might be, in fact, some clustering of events that occurred here towards the end.

Now, this is important to point out because if you've seen studies like this before, you'll see that there are events occurring here around 8 months. We asked people to come back for their angiograms at about 8 months, and, in fact, we see this typically in most trials that require angiography because there's an opportunity to dilate patients that have come back for re-narrowing at this point.

Now, what really happens is that patients generally develop symptoms in this range and that they have tight stenoses if they come back early.

If they have stenoses around the time when their biological narrowing occurs and they have a scheduled angiographic follow-up, they ultimately wait until the patients come back for their scheduled angiographic follow-up to have their appropriate intervention.

How much of these lines might be due to appropriate intervention with the scheduled angiography versus something that might have been an unblinded influence by the operators who actually treat over is something that is difficult to tell. But we can make some inferences about that.

So the mechanism of clustering of those events around the 8-month period is due to the opportunity to treat patients with moderate symptoms and moderate restenosis. That is, generally people have 40 to 70 percent lesions come back with some symptoms, and they generally wait until their scheduled angiogram to come back and get treated.

So they often defer their catheterization from symptoms to the point where they're going to have their planned effect. But the likely reason for higher rates in the control arm at that period compared to the active arm is the fact that the patients who are assigned to the control arm had more frequent 40 to 70 percent narrowings, so we evaluated that per se. And if we look at what we saw from the angiographic narrowing, here are the continuous distribution function curves of diameter stenosis at follow-up. And if you look at the control arm, approximately one-third of the cases had narrowings between 40 and 70 percent, which would be those cases that would be vulnerable to being treated by repeat intervention, most of the time very appropriate.

If we look at the arm for Sirolimus, only about 4 or 5 percent of the cases actually have narrowings in the 40 to 70 percent range, so it's not surprising, if we look back at the zone of angiographic influence, that there were more events occurring in the control arm because there were more narrowings per se, especially at follow-up, compared to the active arm.

The other problem is that if you do look at restenosis at this point here, we think that we are necessarily underestimating the outcomes of both arms and probably diminishing or underestimating the treatment effect, because we're not seeing the true incidence of restenosis that has been deferred or delayed until it occurs right here. So if a study is defined and designed to be measured at 9 months with an 8-month angiographic follow-up just before the 9-month time period, you actually don't get the opportunity to see what really happens in the study by looking back on that curve at 7 months. If we wanted to look at 7 months, we should try to end the trial there, and then we would have the angiographic at 6 months and have a better estimate of the 7-month outcome.

So, in conclusion, the subset analysis, the conventional subset analysis demonstrated a consistent and strong treatment effect for Sirolimus across a variety of important subset categories that have been used in previous stent studies. There was no treatment interaction that demonstrated a patient subset that did not benefit from Sirolimus, and the use of the non-prespecified endpoints, such as the 7.5 clinical restenosis endpoint, especially in this complex study, or nonlinear modelings were not optimal in our analysis to evaluate the outcomes of this randomized trial.

DR. DONOHOE: Mr. Chairman, I just want to present the final three conclusion slides.

Just to summarize the overall safety data from the RAVAL and SIRIUS trials, as we noted, the death and MI rates for the Sirolimus-eluting stent group was comparable to that of the control group. And as we also saw in more detail, there were no deaths in the Sirolimus-eluting group that were considered related to treatment with that stent.

The incidence of stent thrombosis was comparable to that of the bare metal and was, in fact, less than 1 percent, whether 2 months of antiplatelet therapy was used or 3 months was used.

The overall incidence of aneurysms was also discussed. As you saw, there were two aneurysms found at the 8-month follow-up in SIRIUS and one found at the 18-month follow-up in RAVEL, compared to a total of four aneurysms found in the control group. That is, the overall incidence, again, for aneurysms in the active treatment group was less than 1 percent, and there were no adverse events associated with those aneurysms.

We saw that the MACE events for the overlapping of Sirolimus stents was actually lower, significantly lower than at the control group. The data have been generated across a Sirolimus dose range that supports safety of stents up to 33 millimeters in length and over 4.0 millimeters in diameter.

The issue of late incomplete apposition has been observed more frequently in the Sirolimus-eluting stent group. However, it does not appear that it's related to any adverse clinical outcomes, and our plan is to follow these patients over the longer-term 5-year period.

In terms of overall efficacy conclusions, we believe that both randomized studies clearly should support the superiority of the Sirolimus-eluting stent compared to that of the control group on all angiographic IVUS and clinical endpoints. The detailed angiographic analyses do not demonstrate any evidence of an edge effect. The efficacy is maintained across all lesion lengths and vessel diameters tested, as Dr. Kuntz has just presented. We acknowledge there is limited data for vessel diameters above 4.0 millimeters. However, since efficacy has been maintained across all other diameters, it is anticipated that it will still be maintained for diameters greater than 4.0.

The 2-year angiographic and clinical data from the First-in-Man as well as the 1-year clinical follow-up from the RAVEL shows sustained benefit with no evidence of a catch-up effect.

And, finally, in terms of the overall conclusions, we believe the data clearly demonstrate the significant therapeutic benefit of the Sirolimus-eluting stent in the interventional treatment of patients. The clinical benefit we believe does outweigh the potential risks, and the data, we believe, that we presented does support the intended or requested indication, that is, the Cypher Sirolimus-eluting stent is intended for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions of lengths less than or equal to 30 millimeters in native coronary arteries with reference vessel diameters of 2.25 to 5.0 millimeters.

Thank you.

DR. LASKEY: Thank you, gentlemen, for really a lovely presentation.

I think before we--we should probably try to have lunch around 12:30, which would leave -- [tape ends].

-- the sponsor based on this morning's

presentation. Dr. Edmunds?

DR. EDMUNDS: Do you have any autopsy data on the eight patients that died?

DR. DONOHOE: The question was: Do we have any autopsy data on any of the patients that have died? There was an autopsy on one patient who expired in the RAVEL study at approximately 16 months, and this analysis was actually histologic--pathologic analysis was conducted by Dr. Ramani's (ph) lab. This patient happened to have had a bare metal stent placed in a different vessel two years before their death and the Cypher stent placed 16 months before their death. The histologic evaluation included a comparison of the histology in both areas, the bare metal and the Sirolimus-eluting stent.

The findings indicated that actually in terms of local inflammatory response--and the reports of this autopsy have been submitted to the FDA--that there was actually less inflammatory reaction to the Sirolimus-eluting stent and the polymer than there was to the bare metal stent.

There was evidence of re-endothelialization by visual assessment of somewhere greater than 80 percent for the Sirolimus-eluting stent and by visual assessment greater than 90 percent for the bare metal stent. There were no other significant findings in terms of the issues of incomplete apposition or any other significant abnormal histologic findings.

[Inaudible comment.]

DR. DONOHOE: Sixteen months.

DR. LASKEY: Ileana?

DR. PINA: Yes, I have several questions. We've been dealing with coronary disease primarily with our usual revascularization plus drugs. I have seen nothing about what these patients were on. We've been using statins. We've been believing in statins. Now we're using ACE inhibitors to remodel vessel walls. What kind of background therapy were these patients on, number one? Some were on Ticlid, some were on Plavix. Have you analyzed both? In other words, should you get approval, what do we tell the physicians to concomitantly add to the patients and for how long?

DR. DONOHOE: In terms of general medication use, we did collect that information, and we can provide the details of that information. I don't remember the specific distribution, but it's a standard list of antihypertensives, statins, and other cardiovascular type medications. There were no apparent differences between the two treatment groups and the type of medications used.

In terms of antiplatelet therapy, specifically Ticlid and Plavix, I believe in the SIRIUS trial there were only four or six patients who used Ticlid; all others used Plavix. And as I mentioned, the duration was for a total of 90 days.

DR. PINA: Could we see the statin data? Because I don't think that in some of the foreign countries the statin us is as good as it is perhaps in the States, even with as much of a gap as we have.

DR. DONOHOE: Yes, we can provide that to the panel. I don't have it right now. We'll get that information for you.

DR. PINA: All right. May I continue? I have some other questions.

I also looked at your list of sites and the list of inability to deploy the stent in certain sites, and there seems to be a tremendous disparity among sites. I'm assuming that a lot of that has to do with operator experience. But there are some sites that there's really a disparity between the ability to expand the non-coated stent and the coated stent.

Should there be some operator difficulty in one versus the other in actually deploying the stent? I mean, some of the differences were pretty wide. Some have like 75 percent in the so-called control arm and maybe 25 percent in the Sirolimus-coated arm?

DR. DONOHOE: Well, I know there's a variable number of patients entered across the 53 centers, and I assume that the difference in terms of ability to deploy is probably based in part on the technical ability of the operator, but also in terms of the types of lesions that they're treating. It may be somewhat related to types of patient populations, whether the lesions are more heavily calcified or more difficult to expand in general.

We have tested on a number of variables for poolability of the data across these centers, and in terms of the main endpoints of this study and the secondary endpoints, we did not find any evidence that the data could not be pooled. So I would assume that the variation you're seeing is probably more related to the technical issues at those centers.

DR. PINA: So there should be no difference in placing one stent or the other, one being more difficult than the other?

DR. DONOHOE: No. In terms of benchtop testing, there was no difference in performance in terms of the ability to expand the stents or deploy them. And as you saw in terms of the device success number in particular I presented, it's specifically looking at the ability of the operator to deploy the stent, Sirolimus or the bare metal stent, attained less than 50 millimeter diameter stenosis at the end of the deployment procedure, using that treatment stent, that is, the Sirolimus or the bare stent. And as you saw, it was roughly 99 or 98 percent in each group.

So, overall, the success rates were high and comparable between the two treatment groups.

DR. LASKEY: Dr. Aziz, then Dr. Bailey.

DR. AZIZ: This question relates to the diabetic population. Did you break up the diabetic population into Type I and Type II diabetics? And was there more of a beneficial effect seen in one subset versus the other, or are the numbers too small?

DR. DONOHOE: We did break out looking at if we defined Type II as oral diet-dependent type diabetics and Type I as insulin. We did break that out. I believe for the insulin-dependent diabetic group in the active group there were only about 37 to 39 patients, so we're getting down to small numbers. For the oral and insulin-dependent diabetic group, in fact, all the angiographic and clinical endpoints were still significantly improved over the control group. For the insulin-dependent, there was a decrease in the--particularly in segment restenosis rates, and in some of the variables, I believe, in the angiographic there was still some marginal significance, and I think primarily because of the sample size, we lost significance in some of the clinical endpoints.

However, overall, I believe there was still about a 35 percent relative improvement in the insulin-treated diabetics.

DR. BAILEY: Just a clarification. Referring to the blinding, were the angiographers and physicians taking care of the patients aware for each patient whether they had an A or a B stent?

DR. DONOHOE: The investigators taking

care of the physicians were aware whether they re opening an A or a B package. I think I mentioned the packaging, the stents are identical. Holding the stents, looking at them, you can't tell which one has a coating or does not have a coating on it. The angiographic and IVUS core labs, of course, were blinded, as well as the clinical events committee.

DR. BAILEY: So the revascularization decision, the person making that decision wasn't aware of whether it was an A or a B stent?

DR. DONOHOE: On the 9-month follow-up, they would only be aware if they took the time to go look through the charts to see which one the stent--which stent the patient had been assigned to originally.

DR. BAILEY: It seems--it may be a small point, but it would have been, I would have thought, feasible to avoid labeling the stents in that way.

DR. LASKEY: Of course, we'll have additional opportunity to query the sponsor this afternoon, but if there are no other--sir?

MR.   : Yes. Slide 23 that you showed with the blood concentrations, are those average concentrations in the study of 19 subjects? Because--

DR. DONOHOE: They're the two curves you're talking about?

MR.   : Excuse me?

DR. DONOHOE: You're talking about the two curves in the PK study?

MR.   : Yes, the pharmacokinetic. I think it was your Slide 23.

DR. DONOHOE: Those curves were based on means, and I think there were bars at each time point. Let me just check.

MR.   : It was hard to see here. On Slide 22 there were bars, but on the next slide, where you also show the trough, concentrations for the five and the two doses of Rapamune. I'm just asking because those curves were sort of--you know, the Y axis was relatively large for the data that you're showing.

And the reason I'm asking is, you know, do you have any information on drug-drug interactions from your study population in terms of a change in concentration of your drug on individuals who are possibly on inhibitors of, you know, CIP 3a, for example?

DR. DONOHOE: Is this the slide you're referring to?

MR. : Yes.

DR. DONOHOE: Okay. I wonder if I could actually ask someone from Wyeth to come up and address the question about what these levels represent and drug interaction.

DR. ZIMMERMAN: Hello, I'm Jim Zimmerman. I'm the clinical pharmacokineticist in the Clinical Pharmacology Group at Wyeth. Wyeth manufactures and supplies Sirolimus, and we have a business agreement with Cordis.

Now, your question--do you still have a question on this slide, or you want to move on to drug interaction?

MR. : Sort of the first question, you know, has to do with the--in that study population of, I believe, 19 subjects, what was, you know, the variability in the pharmacokinetics, because I think those are just averages that are shown there, but it's hard to see. Because it's a CIP 3a, as you know, there's usually a fairly large individual variability in pharmacokinetics, so the question was: What was the, you know, variability? And then the second question was: Do you have information in terms of the effect of inhibitors of CIP 3a on the whole blood concentration from this product?

DR. ZIMMERMAN: Okay. I understand the second question. I'm still not clear about the first question. You're questioning why those are--we're comparing averages with the single dose--

MR. : The question was: In that Slide 23, are you showing averages and what was the variability? If you're just showing the mean concentration, how, you know, variable were the concentrations that you actually saw in each of the 19 subjects in the pharmacokinetic study?

DR. ZIMMERMAN: Okay. I don't have that information. Actually, the variability--well, I can tell you that the variability in the Tmax's range from about, let's say, one--hold on just a second. I do have that summarized here for you.

Okay. You can't see this on the slide, but the bar at the 1 nanogram per ml goes up to 1.4, and I believe that is a standard--error of the mean?

MR. : I think that is--yes.

DR. ZIMMERMAN: Or a standard deviation.

Standard error of the mean, I believe.

MR. : Okay. And then sort of the second question?

DR. ZIMMERMAN: Drug interactions. I'm quite certain (?) does not have the information on the drug interactions in these studies.

Now, in the development of Sirolimus, we did not conduct intravenous studies--intravenous drug interaction studies. The only information we have is with oral administration. Since you're aware of CIP 3a-4 and p-glycoprotein, the effect of those interactions--those proteins on interactions, you might be aware of Dr. Wesley Bennett's work in which he indicates that the effect of the extraction of Sirolimus in the gut is about twice as great as it is in the liver. Also, the effect of ketoconazole, an inhibitor, and rifampin, an inducer, is also about twice as great as it is in the liver.

So although I could show you the large magnitudes of the interaction, for example, with ketoconazole and Sirolimus is about--almost a thousand-fold increase in concentrations; however, that does not translate--you can't translate that to the IV situation. It's probably about 50 percent of that after an IV.

Now, what about the clinical significance of drug interactions? I don't think the clinical significance is great, even for a drug like ketoconazole, because the concentrations are so low. You're looking at a concentration at peak of either 0.5 to 1 nanogram per ml, and even increasing that five-fold still has you in a very safe region for systemic exposure of Sirolimus.

MR. : How about in terms of, you know, pharmacodynamic drug-drug interactions? When you look at the drug label for the compound, there's a black box warning for, you know, concurrent use with cyclosporin, for example. It's probably not pharmacokinetic, and it's probably a pharmacodynamic effect. Can you comment on the applicability of the drug label in terms of, you know, combinations of drugs in terms of this device?

DR. ZIMMERMAN: I have not seen that labeling, but we know that the immunosuppressive effect of cyclosporin and Sirolimus is not strictly additive. There is an increased effect after administration. The two drugs together give you a greater immunosuppressive effect than Sirolimus alone or cyclosporin alone.

MR. : If I can just ask one more question, Mr. Chairman. The question, I guess, for the company, for the sponsor, would be how much of the drug label do they plan on incorporating in the instructions for use and the device label, and specifically, just so that you can find it, in our packet it's in Tab 3.3.1, page 11, it has the black box warning in terms of a contraindication for hepatic artery thrombosis when those drugs are used together. So I guess the question is how much of the drug label are you planning on incorporating in the instructions for the device.

DR. ZIMMERMAN: I think I'll let the sponsor answer this.

DR. DONOHOE: I think actually the draft IFU that is in your packet is--at this point we thought was probably sufficient in terms of some of the issues you're raising. We believe there is a very low concentration with minimal clinical significance of interaction, and I believe there's potentially a question that comes up later FDA will present to the panel, further discussion or input from the panel on that.

MR.   : So you're saying that--I mean, as I see the instructions here, there really isn't anything in terms of drug information.

DR. DONOHOE: Drug interaction data, yes.

MR.   : Okay.

DR. LASKEY: And I think we'll return to that this afternoon as well.

One final question.

DR. PINA: Following on that same track and based on the question that I asked you before about the statins, Sirolimus is known to increase lipid levels, triglycerides quite substantially, and cholesterol kind of do track. And obviously the levels that I see here are much lower than what I would use in a transplant patient, but I think we need to see some data about what happens to triglycerides and what happens to lipids in general, and, therefore, the statin question comes back again as being, I think, rather important in your advice to physicians when they're going to employ this therapy.

DR. DONOHOE: In the two studies I presented, RAVEL and SIRIUS, we actually didn't measure cholesterol or triglycerides following the index procedure or over a length of time following the procedure.

I believe the data that's been generated on the effect of Sirolimus on lipid levels generally indicates that usually you start to see an increase between one and two months after starting therapy, and also that the relative increase of both triglycerides and cholesterol was proportional to the dose. At the 1 milligram oral dosing with Sirolimus, it was found that numerically there was an increase in triglyceride and cholesterol, but not a clinically significant increase. And that increase or relative delta kept increasing with the higher dose. So the reason we did not collect triglycerides and cholesterol over time is based on that information we would actually expect no impact on triglyceride or cholesterol levels, given the variables we're dealing with and given that it typically takes one to two months of constant daily administration to increase those levels.

DR. PINA: But you may be dealing with a population that already has as one of its most significant risk factors hyperlipidemia, which we don't know. I mean, these are [inaudible] a little bit different than, you know, a dilated cardiomyopathy that comes to transplant and may have normal triglycerides to start with.

DR. DONOHOE: Agree. Although I think generally--and if anyone from Wyeth has any more details on this, my impression is that whether you're starting with low or elevated, patients were still at risk for continued elevation, and that these levels for short duration of exposure, I wouldn't expect to have any--certainly any long-term elevated lipids, even with oral dosing. I believe once dosing stops, the lipids do decrease.

DR. LASKEY: I just have one burning question, which is the flip side of this. Many of our patients are started on Hmg-CoA inhibitors at the time they leave the hospital following the intervention. Is there anything we should know about or speculate on in terms of the effects of rapamycin on hepatotoxicity or myositis, et cetera, et cetera, the side effects of Hmg-CoA inhibitors initiated simultaneously? Everything is thrown at these patients on their way out the door, oftentimes.

DR. SCIROLA: I'm Dr. Joseph Scirola (ph) from Wyeth. As you heard, Wyeth is the supplier and manufacturer of Sirolimus, and we have a business agreement with Cordis.

The issue of interaction with Hmg-CoA is very, very relevant because of the fact that Sirolimus raises both cholesterol and triglyceride levels. And in our pivotal trials which were shown, approximately 60 to 70 percent of the patients actually ended up on lipid-lowering agents, and for the most part they were Hmg-CoA reductase inhibitors.

We've looked, not only in these studies but other studies, at the potential interaction, not only pharmacokinetic but toxic interactions, and we have not found an increased incidence of rhabdomyolysis. In fact, of the few cases that have occurred, there have been other explanations.

We also have an interaction study with aturostatin (ph), and there is no drug interaction between Sirolimus and aturostatin.

DR. LASKEY: Thank you.

I think the better part of discretion here would be to break for lunch at this point, and we'll come back in exactly one hour at 1:30 for the FDA presentation. Again, thank you very much.

[Luncheon recess.]

A F T E R N O O N S E S S I O N

DR. LASKEY: If we may, I'd like to reconvene, please. Thank you very much.

FDA, are you good to go?

MS. FOY: Yes.

DR. LASKEY: All right. We'll resume today's panel session with the FDA Presentation.

FDA Presentation

MS. FOY: Good afternoon. I would like to thank you all for reconvening with us this afternoon.

My name is Joni Foy, and I am a biomedical engineer in the Interventional Cardiology Devices Branch in the Office of Device Evaluation, in the Center for Devices and Radiological Health. I am also the lead reviewer for the Cypher Sirolimus-Eluting Coronary Stent System, original PMA submission P020026..

Today, myself, Dr. John Hyde, the lead medical officer, and Dr. Murty Ponnapalli, the lead statistician, will present the FDA's summary for this product, which is the Cypher Sirolimus-Eluting Coronary Stent System.

I did want to mention that this product is the first coronary drug-eluting stent to come before the Panel for the treatment of de novo lesions in native coronary arteries. Additionally, the Cypher drug-eluting stent product is a combination product because it consists of a device and a drug component. As such, this PMA submission has been extensively reviewed in conjunction with the Center for Drug Evaluation and Research.

As a Panel participant today, you are being asked to discuss and make recommendations on the applicant's PMA submission. Your points of discussion of the clinical study results and labeling recommendations will be taken into consideration by the FDA in the evaluation of the application.

Finally, you will be asked to vote on the approvability of the product that was tested clinically.

To give you a brief overview of our presentation, we will briefly discuss the following. I will identify the FDA Review Team members; I will provide a brief summary of the description of the product; I will also provide a brief summary of the nonclinical evaluation and summarize the major outstanding nonclinical issues to date. John and Murty will provide a summary of the clinical and statistical evaluation of the Cypher product; and then we will identify the FDA questions for the Panel to discuss.

I would like to take this time to actually acknowledge the extensive review team that has been associated with this product. You can see that there are a number of individuals. Members from the Center for Devices and Radiological Health include myself. I am a biomedical engineer, and I am the lead engineer and reviewer, from the Office of Device Evaluation.

Dr. John Hyde is a medical officer and the lead medical officer for this project. He is also a statistician, and he is from the Office of Device Evaluation.

Dr. Nick Jensen is the lead animal reviewer from the Office of Device Evaluation.

Dr. Neal Muni is a visiting medical officer to the Office of Device Evaluation, and he assisted with the review of the IVUS data and the death reports.

Dr. Murty Ponnapalli is the lead statistician from the Office of Surveillance and Biometrics and served as the statistical reviewer.

Mr. Doyle Gant is a biomedical engineer

from the office of Device Evaluation who assisted with the ISO 10993 biocompatibility review.

Dr. Scott McNamee is a materials engineer from the Office of Science and Technology and assisted with the polymer chemistry review.

Mr. John Glass is the lead compliance/manufacturing review from the CDRH Office of Compliance, Division of Enforcement 3.

Mr. Rodney Allnutt is from the Office of Compliance, Division of Bioresearch Monitoring.

The lead scientific reviewers from the Center for Drug Evaluation and Research are the following:

Dr. Xiao-Hong Chen is the lead chemist from the Office of Pharmaceutical Science, Division of New Drug Chemistry I, who actually reviewed the chemistry, manufacturing and controls of the drug substance and polymeric coating.

Dr. Patrick Marroum is a pharmacologist from the office of Polymer Science, Division of Pharmaceutical Evaluation I, who reviewed the pharmacokinetics and dynamics and human PK study.

And Dr. Belay Tesfamariam is a pharmacologist from the Office of New Drugs, Division of Cardio-Renal Drug Products, who assisted with the biocompatibility/toxicity review of the animal data.

I would also like to take this time to acknowledge other members who are not listed on this, because this is the only opportunity to give them some public recognition.

Dr. Albert Defelice is a pharmacology team leader from CDER; Dr. Kasturi Srinivasachar is the chemistry team leader from the Office of Pharmaceutical Science, Division of New Drug Chemistry I; and Dr. Doug Throckmorton, who is Director of the Division of Cardio-Renal Drug Products; Mr. Don Serra [phonetic], who is the Chief of Cardiovascular Products, Division of Enforcement III; and Dr. Gary Gray, who is the team leader, Cardiovascular and Ophthalmic Products.

In addition, our administrative staff and our upper management, including Ms. Ashley Bellum, who is the Chief, ICDB; Dr. Donaby Tillman, who is Deputy Director for Cardiovascular Products; Dr. Bram Zuckerman, who is the Division Director; and Dr. Dan Schultz.

[Slide.]

That being said, let's get to the heart of the matter. I wanted to lay out a regulatory history that has been associated with the Pre-Market Approval application for this product.

This application was actually reviewed under the PMA Modular Submission Program, and that actually means that sections or modules of the application can begin to undergo substantive review prior to submission of the last aspect of the formal PMA submission. In this case, the complete clinical cohort for the SIRIUS study was that last component.

I wanted to also note that even though the Center for Devices and Radiological Health is officially designated as the lead center for this combination product as part of an official request for designation from the applicant, appropriate sections of this application have been and will continue to be reviewed in conjunction with the Center for Drugs and Evaluation Research.

The Agency would also like to mention that the review of this product has been very interactive between the Agency to appropriately and timely identify issues, and the application to respond to these concerns.

Module I was the Quality Systems and Manufacturing Controls module. Since CDRH has the lead for this combination product, CDRH compliance also has the lead.

However, CDER also has the authority to inspect the manufacturer of the drug substance for compliance with current Good Manufacturing Practices. Inspections of the manufacturing facilities are currently underway.

The Chemistry, Manufacturing and Controls model, or CMC as we will be referring to it, was subsequently reviewed by the Agency. This information was jointly reviewed by both CDRH and CDER.

And lastly, Module 2 contained the bulk of the nonclinical testing that was submitted to support the application as well as an interim clinical summary of the SIRIUS study as well as studies of the RAVEL, First-in-Man, and PK studies.

I also wanted to denote, as the sponsor has previously indicated, that the last component of the modular submission was submitted to the Agency on June 28, 2002 and was designated as the original PMA. This component contained the clinical report for the full cohort of patients enrolled in the SIRIUS study, the 12-month data from the RAVEL study, and the available 18- to

24-month data from the First-in-Man study, as well as the data from the PK study, and the applicant's versions of the updated labeling and the Summary of Safety and Effectiveness Data.

Sine all of the modules were still under active review by the Agency and responses pending by the applicant at the time of the PMA submission, all of the modules were actually closed and rolled into the PMA application and subsequent issues addressed as part of the PMA review.

Sine this application was granted expedited review status, the Agency completed their review of the PMA and all amendments submitted by the applicant by September 3. Based upon our review of the information provided, the Agency issued the applicant a Major Deficiency Letter on September 18, 2002. A Major Deficiency Letter is one of the letters that can be issued by the Agency to request additional information from the applicant, which is deemed necessary to complete the review of the submission.

The applicant submitted their official response to the Agency's letter yesterday, on October 21, 2002. Obviously, the Agency has not had an opportunity to review this response for its completeness or adequacy in addressing the currently identified outstanding issues and information that may be been included in this amendment are not included within the Agency's presentation today.

The Agency and the applicant will continue to work interactively to resolve the outstanding issues previously communicated to the applicant for this application.

I want to briefly give you a product description as defined by Title 21 of the Code of Federal Regulations, Part 3, the Cypher Sirolimus-Eluting Coronary stent is a combination product, because it is comprised of two regulated components, in this situation, a device and a drug.

The device component for the Cypher stent consists of the following: The Bx Velocity, balloon-expandable, 316L stainless steel stent. The Bx Velocity, as already articulated by the applicant, is currently approved for use in de novo or restenotic lesions, less than or equal to 30 mm in length, in native coronary arteries with reference vessel diameters from 3.0 to 5.0 millimeters.

The Bx Velocity stent is also approved for the treatment of abrupt or threatened abrupt vessel closure in lesions less than or equal to 30 mm in length, with reference vessel diameters from 2.25 to 4.0 mm.

The Bx Velocity stent is approved on both of the delivery systems proposed--the Raptor over-the-wire and the RaptorRail Rapid Exchange version.

Only the Raptor Over-the-Wire delivery system was used during the SIRIUS study. Both the Over-the-Wire and Rapid Exchange systems are the subject of this PMA application.

To make the Cypher product a combination product, the applicant has coated the Bx Velocity 316L stainless steel stent, both luminally and abluminally, with a drug/polymer coating.

The proprietary coating process consists of a layered mixture of non-erodible polymers to which the drug substance is added.

A drug-free topcoat is applied to the stent surface to influence--in other words, slow--the release kinetics of the drug from the surface.

The drug substance used in this product is manufactured by Wyeth Pharmaceuticals.

Sirolimus is the drug substance.

Rapamune, which is Wyeth's trade name, is approved by the Agency in both tablet and oral solution formulations as an immunosuppressive.

The applicant has leveraged the initial drug substance safety data provided in Wyeth's NDAs in support of this submission.

Sirolimus has not been approved for the treatment of restenosis or for use in coronary arteries.

The applicant refers to the product with the drug-free topcoat as the IXTC, or the slow-release formulation, whereas product without the topcoat is referred to as the IX or fast-release formulation. All patients in the treatment group of the SIRIUS and RAVEL studies received the IXTC or the slow-rate-release formulation, and the applicant is currently seeking marketing approval for the IXTC formulation.

I wanted to expand a little bit on a previous slide that was presented by the sponsor. As you can see, for this PMA application, the applicant is actually requesting approval for the following stent sizes designated in this matrix--diameters from 2.25 to 5.0 mm in lengths of

8 to 33 mm, with the exception of the 5.0 x 8 mm diameter stent size.

Please note that the drug and polymer content vary as a function of stent size.

Based upon the dose density of 140 micrograms per centimeter squared of metal surface area, the total nominal dosage of sirolimus ranges from a minimum of 71 micrograms to a maximum of 399 micrograms for the currently proposed matrix of stent sizes and is shown on this slide in white text.

The total nominal dosage of polymer content ranges from a minimum of 208 to a maximum of 1,184 micrograms for the currently proposed matrix of stent sizes and is shown on the slide in red.

As denoted in yellow on this slide--it is kind of hard to see, and I don't have a pointer--you will see that the SIRIUS and RAVEL studies were conducted using the 2.5, 3.0 and 3.5 mm stent diameters in lengths of 8 and 18 mm.

The inclusion criteria for the RAVEL study included lesion lengths of less than or equal to 18 mm, whereas the SIRIUS study included lesion lengths between 15 and 30 mm inclusive in length.

Consequently,a s part of the SIRIUS study, the applicant was able to implant two stents, which theoretically accounted for up to 350 micrograms of drug and up to 1,040 micrograms of polymer in a small subset of patients. The Agency has concerns over the lack of chronic preclinical and/or clinical information to support the safety of the amounts of drug and polymer on the larger and longer sizes of the proposed stent matrix. The yellow right here denotes the stents that were actually implanted in the SIRIUS and the RAVEL studies.

The last point that I wanted to mention was that the Agency does have concerns over the lack of chronic preclinical and/or clinical information to support the safety of the amounts of drug and polymer on the larger and longer sizes of the proposed stent matrix.

I wanted to briefly touch on the nonclinical evaluation conducted by the sponsor. In vitro preclinical pharmacology studies and in vivo release studies, as outlined in Section 1.6 of the FDA summary, were performed by the applicant to assess the elution kinetics and toxicity of the Cypher product.

Although effectiveness is demonstrated through human clinical trials, animal studies can actually provide important information such as detailed arterial histopathology and histomorphometrics, which are not obtainable through human clinical experience.

` In vivo animal testing, as outlined in Section 2 of the FDA Summary, were conducted on porcine coronary arteries, for the clinically-intended dosage and overdosage. The Agency will consider the animal study data when evaluating issues related to the long-term safety of the requested range of drug and polymer dosages.

Biocompatibility testing in accordance wit ISO 10993 was conducted on polymer-coated stents or coupons, without the inclusion of the drug substance. Since the applicant did not actually conducted ISO 1-993 testing on the finished product with drug substance, a chronic porcine implant study was utilized instead using finished product with drug to evaluate the biocompatibility.

Bench testing as outlined in Section 1.4 of the FDA Summary was performed to evaluate the mechanical integrity and function of the Cypher product.

As outlined in Section 1.8 of the FDA Summary, the applicant has only submitted limited data, which does not adequately support the requested shelf life at this time.

To assess coating integrity, the applicant has performed drug content, elution, degradation impurity, residual solvent and particulate testing of the finished Cypher product. Although issues have been identified with coating durability on the bench and in animals, the potential implications on clinical outcomes are being assessed by the applicant.

As outlined in Section 1.7 of the FDA Summary, the Agency is unable to ascertain whether there is an effect of sterilization method on the finished product at this time.

To date, there are unresolved issues pertaining to the nonclinical testing submitted by the applicant in support of this submission.

No data have been presented that indicate a clear safety concern in the clinical setting regarding mechanical device failure or malfunction., specifically talking about coating integrity issues.

I also want to take this opportunity to

identify some of the major outstanding concerns that we previously articulated to the sponsor in their Major Deficiency Letter.

Several of these nonclinical issues are of note, and the reason why I have put these here is because they directly have an influence on the safety and effectiveness of the manufactured product. They are briefly summarized here.

The first of these is an in vitro elution methodology. The development of an acceptable, discernable in vitro elution methodology and specifications are critical for adequate characterization of the product tested clinically as well as to evaluate consistency in a commercially-manufactured product. Ideally, the in vitro dissolution specifications should encompass the time frame over which at least 80 percent of the drug is eluted or where the plateau of resolution is reached if incomplete leaching is occurring.

The in vitro elution method is also important in establishing the stability data for the product. The ability of the in vitro assay to predict in vivo elution is valuable in evaluating the significance of future modifications to the product, such as a change to the coating process.

The Agency is aware of the challenges faced by device manufacturers in the appropriate development of in vitro assays for drug elution given the nature of the drug, and the Agency is working interactively with the applicant in the development of an appropriate methodology via both a short-term and a long-term solution.

The second data point here is the stability. Based upon the lack of supporting data which should include at a minimum drug elution and impurities, the Agency has not been able to assign an expiration date to this product at this time. The collection of stability data to support a shelf-life for the product is currently ongoing by the Applicant.

Additionally, the Agency was recently notified of a modification to the coating process. The Agency is concerned that the changes to the coating process could influence multiple parameters of the manufactured product, such as elution, coating integrity, impurities, et cetera, and the applicant would need to be able to verify that the product tested clinically has the same characteristics as the commercially manufactured product. The Agency is currently reviewing this modification and assessing the need for additional testing.

Once again, I would like to emphasize that the Agency is working interactively with the applicant to adequately address these issues in addition to the other issues previously identified. As previously indicated, the applicant did provide a written response yesterday to the Major Deficiency Letter which was issued on September 18. The Agency will review this supplemental information in a timely manner and work interactively with the applicant to resolve any additional outstanding nonclinical issues.

This was previously articulated by the applicant. The applicant has proposed the following indications for use for the Cypher Sirolimus-Eluting Coronary Stent system:

Improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete de novo lesions in length less than or equal to 30 mm in native coronary arteries with a reference vessel diameter of 2.25 mm to 5.0 mm.

As previously indicated by the applicant, the First-in-Man study was conducted in de novo vessels where the inclusion criteria was reference vessel diameters of 3.0 to 3.55 mm inclusive and lengths less than or equal to 18 mm in length.

The RAVEL study was conducted in de novo vessels where the inclusion criteria was reference vessel diameters of 2.5 to 3.5 mm inclusive and lengths less than or equal to 18 mm in length.

The SIRIUS study was conducted in de novo vessels where the inclusion criteria was reference vessel diameters of 2.5 to 3.5 mm inclusive and lengths less than or equal to 30 mm in length.

Now Dr. John Hyde will come to the podium and address some additional specifics about the clinical performance of the Cypher product that was tested clinically.

DR. HYDE: Thank you, Joni.

My name is John Hyde, and I was the medical reviewer on this product.

First of all, I don't intend to go over the principal results of the clinical studies. I think Cordis did a good job of presenting those results. So the purpose of my talk today is really just to present some of the issues that the FDA identified in the course of the review. Some of these issues are not really problems per se, but represent aspects of the design or endpoint definitions that we feel you should keep in mind now during your deliberations. And many of these issues we have also raised to the sponsor, and in some of those responses, I see they have provided some serious and thoughtful responses to today that we have not had an opportunity to review in detail.

Some of the other issues go to how broadly we can construe the indications, in other words, how well the data support extensions of the findings to the borders of what was studied clinically.

In a sense, these are really second-order phenomena. We don't really have any dispute over the overall positivity of this study. I think the Sirolimus effect is fairly clearcut. And in fact, I think it speaks well to the study that we have already been in a position to raise some of these issues and have the potential to address them.

[Slide.]

This is just a recap of the supporting clinical data that were provided in this application. The SIRIUS study, in which 1,058 patients were available for or provided evaluable data, was strongly positive if used as the primary endpoint, the clinical endpoint of target vessel failure at 9 months.

The RAVEL study, with 238 patients, also was strongly positive. It used the primary angiography endpoint of late loss, but it also collected clinical date, and we have target vessel failure at a year as important clinical information from that.

The PK study was really just a small study with short follow-up, but it did demonstrate that there is a fairly long elimination half-life in humans, more so than just the drug substance itself, which suggests it sticks around on the stent for a while, or any area of the stent for a while. But it doesn't really provide much more than just short clinical follow-up.

And finally, the First-in-Man study, which had 45 patients, 15 of those were with the alternate formulation, so 30 patients actually had the clinically proposed formulation, and although it is a small study, it is the one that does afford us the longest followup to date, out to 2 years.

In addition, there are other clinical studies that are ongoing and under way, but they were not provided in this application in any detail that we could review.

The clinical data, then, really come primarily from the SIRIUS and RAVEL studies, and let me just contrast them.

They were very similar in many of their design features, but there are a couple of differences to keep in mind. One is that the RAVEL really had shorter lesions. They all had to be covered by the 18 mm stent, whereas the SIRIUS allowed lesions as long as 30 mm. The RAVEL study also used much less IIbIIIa inhibitors during the procedure, only about 10 percent or so in contrast to the SIRIUS study, which used about 60 percent.

And also, although they both had antiplatelet drugs following mostly plavics, the RAVEL study used it for 2 months, and in the SIRIUS, it was used for 3 months.

[Slide.]

I'm just going to recap some of the efficacy issues. Some of these, there isn't really too much more to say other than to bring them to your attention, and some of the others, I'll have a little more to say on later in the talk.

First of all, as was already mentioned, both of these used an A-B scheme; in other words, they were assigned Lot A, and they took the A package out of the closet, or the B--although for logistics reasons, it is quite understandable why this was done, because you don't know exactly what size you're going to use, but it does, of course, have the risk that if even one patient is unblinded, the entire scheme has the potential for being unblinded.

In the RAVEL study, randomization was accomplished by distributing envelopes to the centers, which of course has the risk that this assignment might be uncovered, or that concealment of assignment might be compromised with that particular situation.

The SIRIUS study used a central randomization scheme.

And finally, we don't meant to imply that we feel the study was not blinded properly, but we don't really have the information to address what the quality of the blinding was. There was no retrospective assessment of whether people knew the assignment or what they thought the assignment might be, so we just can't address that issue.

And finally, in the SIRIUS study, as was mentioned earlier, there was a "deregistration" of some patients. About 5 percent of patients in each arm were deregistered, which means that after the randomization assignment, it was determined that they really shouldn't be in the study, and they did not receive a stent and then were not followed up, so we really don't have followup information on those patients.

On review of most of them, it does appear that they objectively did not meet certain eligibility criteria, but on the other hand, there were many patients in the study who didn't quite meet the eligibility criteria, either, so that wasn't necessarily consistently applied.

I guess as a worst case, you could say that the differences you see might be 4 percent less, but still, they are usually pretty strong.

Okay, I don't really have much more to say to address that issue.

[Slide.]

These are three of the four issues that I will be talking about a little bit more subsequently. One of them is the influence of angiography on target vessel failure, TVF, and the Cordis presentation mentioned that, and I have some comments on that later; the effect of lesion length was addressed, and I will talk about that a little bit more, as well as the effect of vessel diameter.

[Slide.]

Another issue is the effectiveness for vessels of diameter less than 3 mm. I know this is partly regulatory and partly science. Both of these studies compared the Cypher stent to the bare stent over the full range of vessel diameters, which was targeted to be 2.5 to 3.5 mm. However, the bare stent does not have FDA approval for de novo reasons in vessels of diameter less than 3.0, and therefore, superiority to a bare stent in those cases is not really prima facie evidence of effectiveness, so we need to supplement that finding with some additional information. In particular, a separate analysis was done for small vessels, and Dr. Ponnapalli is going to present that analysis subsequently and draw on historical angioplasty information using a Bayesian analysis.

And also, just keep in mind that any of the other overall comparisons we are going to be looking at are including these small vessels and involve comparison to the not necessarily approved control in that range.

[Slide.]

A couple of safety issues to keep in mind--one is late malapposition. Cordis presented some data on that, and I will be recapping that near the end of my talk. And some other issues--these are just things to keep in mind; I don't know that we have anything specifically to be able to address these, and we have asked the sponsor to look at these in addition.

One is that there are higher dosages with longer lengths and particular with the larger-diameter stents, as Dr. Foy pointed out. The sponsor is interested in a fairly broad range of lengths and sizes, some of which would use total doses that exceed what was studied in the clinical studies.

Another question has to do with overlapped segments. In places where two stents are used, there is an area of overlap in which case the dose density would be higher. About a quarter of the patients I think fell into that group on analysis of clinical data, and that subject didn't identify anything, but we have asked the sponsor to see if there is anything on imaging targeting specifically that overlap segment that could be informative.

Finally, we do not have any information on the interaction with brachytherapy, either, using a stent in a patient who has been treated with brachytherapy or using brachytherapy subsequent to treatment with stent.

And finally, some issues--and I think the panel has already raised some of these questions--on what the potential for systemic toxicity is. Although the drug concentration is at a fairly low level, there is some sustained exposure to Sirolimus after the stent is placed, and one question is what should be our level of concern about that, and what have we learned about that.

In the SIRIUS study, the sponsor did look at hematologic dysplasia, at least for the course of the hospitalization and did not notice any difference between the other groups, but as was mentioned, things like effect on lipids were not evaluated.

[Slide.]

Finally, a couple of other issues, and these are just things to make sure you are aware of. One has to do with the definition of MACE that was used in the studies. MACE did not include target vessel revascularizations that did not involve the target lead. Target vessel failure did include these, so there is a slight difference in the rates. MACE is about 1.5 to 2 percent lower than target vessel failure because of that definition.

And secondly, Cordis changed the definition of MI from what was proposed in the protocol based on CKME to the WHO definition based on total CK. The practical impact of that is that it lowers the MI rates by about 4 or 5 percent. We don't view this as issues causing particular bias, because they are applied uniformly across both groups, but they do bear on how you might compare these to your historical experience, and in particular, there are some questions outstanding relating to the Bayesian analysis which was based on these rates.

[Slide.]

Now I'd like to talk to talk a little more on four of these issues, one of them being the influence of angiography on target vessel failure as I think Cordis mentioned. That was one of the issues that we had raised.

Here are some of the points points on that. First of all, the endpoint of target vessel failure was really mostly revascularization. There were some deaths and MIs, but the majority of events were revascularizations, and therefore, there is some discretionary component to that.

Now, ideally, the FDA strongly prefers to have a clinical endpoint as opposed to a laboratory finding or an indigenous study to form the basis of a finding of effectiveness, and to the extent that the angiographic results may have influenced the clinical endpoint and there is some dilution of the clinical meaningfulness of TVF as an endpoint, as the sponsor mentioned, the events were adjudicated by a Blinded Events Committee, and that certainly is a helpful way to address that.

So one other thing we proposed looking at with a sensitivity analysis was also to look at the TVF rates at a time point preceding angiography, which would be about 7-1/2 months before the [inaudible] angiography was scheduled. That does have the disadvantage, though, of fewer events at that point, and it isn't necessarily pure, either, in that the anticipation of an angiography may somehow affect the results. But it does give you another way of looking at the data as sort of a sensitivity analysis, and I think you have already seen these--I am going to go over them quickly.

[Slide.]

This is the TVF-free survival in the SIRIUS study. You may not be able to see it too well. It covers the 9-month period of the study from left to right, and the dotted line is the control or Bx velocity stent [inaudible] Sirolimus, and you can see a progressive separation of the curves over time, but particularly one month before the end, there is a marked drop particularly affecting the control group, and this is at the same time point as the angiography was done, so that in particular this seems to affect the control group more than the other. So one thing we did was look at slightly before that time point to see if that really made any difference in our interpretations.

[Slide.]

There is a similar phenomenon seen in the RAVEL study. This covers one year of the study, and you notice that about halfway along there, the control group has a significant drop, and that coincides with the 6-month angiography endpoint. So there seems to be at least some temporal evidence that there is some bearing on the vascularization endpoint from the angiography findings.

[Slide.]

So what we did was an analysis that looks at the 7-1/2 months as well as the 9 months, and you can see from this, although you expect smaller rates at 7-1/2 months, there is still a preservation of the treatment effect. It isn't as large in absolute terms, but there is still at least a twofold difference in target vessel failure rates even looking at it at this point. So the study is pretty robust in this respect--although as we stress the data a little more and look at some of the issues I'll talk about later, using 7-1/2 months may have more impact.

[Slide.]

Another thing to consider, as I mentioned--because the control stent was only approved for 3 mm diameter and above, I also looked at the subset that had 3 mm and above as sort of a pure test of efficacy, and even in this situation, there is statistical evidence of a significant treatment effect of about the same relative odds--at least a doubling of the rate on the control group compared to Sirolimus.

[Slide.]

I'd like to take a couple of minutes to talk about the issue of lesion length. Cordis present some information on that previously. And basically, if there is any information that was provided in the clinical summary--this is sort of the ageless problem of trying to get the most you can from the data, sort of stretching the data of what the clinical experience was--so to some degree it is statistics, to some degree it is an art--some might argue that it's a black art, and they may be right.

So anyway, I am going to present some of the modeling I did at least on the data that was originally presented to us, and there is certainly a subjective element to this, so I am offering this as one end of the spectrum. I see that Cordis has done some additional analyses to address this, and they have done some other thoughtful things, but we did ask them to address this issue, but I'm not going to speak directly to what they said today.

[Slide.]

Here is our take on lesion length, and again, I think additional analysis could be informative here. The initial thing that we looked at--we did not take into account some of the multivariate modeling, and that could be enlightening.

But just to recap what the issues are, the target range by the eligibility criteria in the SIRIUS study was that the lesion lengths should be 15 to 30 mm. It turned out that about 80 percent of cases actually fell lower than that, in the 8 to 22 mm range. This is using the quantitative coronary angiography assessment of lesion length rather than the visual estimate by the investigators. So there is some missing of the target incidence on that, and even by the visual estimate, there was certainly a strong clustering of the lesion lengths toward the low end of the target range.

The second is the issues I mentioned before--the incidence of TVF versus angiography--and I think there is some discordance in the conclusions that might come through looking at the effective lesion length on those endpoints. The core issue, then, is what is the confidence we have in extending the findings of this study to the longer lesions.

I should say that RAVEL doesn't really

help us address this, because they only targeted lesions that could be covered by the 18 mm stent, so they don't really even have long lesions in that study at all; it really all pretty much comes from the SIRIUS study.

[Slide.]

This is a graph that shows the binary restenosis rate. This is the angiographic endpoint of assessment of whether or not there is greater than or equal to 50 percent stenosis in the angiographic subset, which was over three-quarters of the patients.

The horizontal axis is lesion length as measured by quantitative angiography. And what is plotted here is the open circles are the control group, showing restenosis rates rising from 30 to 60 percent over the range that is plotted here; and the solid circles down below are the Cypher rates.

Interestingly, the control rates tend to be higher than the target vessel failure rates, considerably, and the Cypher rates actually tend to be somewhat lower than the target vessel failure rates.

I have plotted here error bars which represent 1.5 standard errors of the regression estimate, and here I have just used a simple linear logistic regression. So these are not subgroup analyses per se, these represent the model estimate.

I used the 1.5 because there is an approximate correlation between overlapping of bars at that length and the finding of a statistically significant difference. But I think the message from here is that even for fairly long lesion lengths--and there aren't a lot of patients out there above 30--that using a binary restenosis endpoint, there seems to be a good separation between the groups.

[Slide.]

That is somewhat in contrast, though, to what you see if you look at the more clinical endpoint, the primary clinical endpoint of 9-month target vessel failure. This plot is similar in design, with the quantitative angiography lesion length along the horizontal axis, and the TVF rates for the vertical axis. Control again is the open circle, Cypher is closed. The error bar is 01.5, standard error is open model estimate.

The model that was used here, though, is something a little more complicated than the linear model. In fact, I wound up using cubic regression models to fit these data. Now, certainly there is a subjective element to this, and there is not necessarily statistical significance of all the terms that were added into this model. However, as I said, I didn't consider the linear model necessarily to be my null hypothesis here, and this is partly a result of just some subjective modeling to try to see what really seemed to fit the data using some other things on top. So this is a subjective analysis, but I think it has fairly good fidelity to the data.

And what this seems to indicate, anyway, is that certainly in a range of where most of the cases fell, to about 20 or so, there seems to be strong evidence of a treatment effect for Sirolimus, but that as you get to longer lesion lengths, there becomes some question of how well-separated they are. Although the estimates certainly show a persistent treatment effect of smaller magnitude, the uncertainty because of smaller numbers makes it less a clear separation as you saw, for example, with the angiographic endpoint.

[Slide.]

Further, if you choose to use the 7-1/2-month target vessel failure rate that we talked about earlier, not surprisingly, with lower rates and thus smaller difference, they even seem a little closer together here.

[Slide.]

The purpose of this slide is to underscore some of the problems you get to when you select subgroups and emphasizes why I really went more with a holistic modeling type of approach rather than subgroup analysis.

If you look at the subgroup of lesion length greater than or equal to 25, there are only 51 patients total. That means about equal in both groups. And there is certainly a large treatment effect, but the confidence in that is somewhat muted.

For lesion lengths greater than or equal to 20, there is a reasonable sample size, and there appears to be a strong treatment effect; but interestingly, if you pick your cutoff somewhere else, 18 or 16, for example, it is a little less clear. So again it goes back to the black art of trying to decide how to look at these subgroups properly. It is partly for this reason that I chose to try to fit a model of that and look at subgroups.

[Slide.]

Next, I would like to turn to the issue of vessel diameter. Again, the issues are pretty much similar as they were for lesion length, just with another variable. And again I offer what was presented in a clinical summary as one end of the spectrum, one way of looking at these data, and the sponsors presented some additional analysis as well.

One thing to keep in mind is the proposed stent lengths run the gamut from 2.25 all the way up to 5.0, even though the eligibility criteria were a smaller range than that and certainly, the clinical data didn't quite encompass that range, although there are always individual patients that fall outside that, so the question is what can we learn from that.

The issues with the reference vessel diameter are that the SIRIUS target range was 2.5 to 3.5 millimeters, and I think they came pretty close in that 80 percent of cases were in the 2.2 to 3.4 or a little lower. This is again using the quantitative coronary angiography assessment of vessel diameter which tends to be a little smaller than the visual estimate by about 10 percent or so. And again, the issue, then, is what is the confidence of extrapolating, in particular the issue would be to large vessels. Small vessels, as I mentioned before, because of the nonapproval of the control stent for small vessels, has some of its own special issues. And Dr. Ponnapalli I hope will talk about that next.

[Slide.]

This chart, similar to what was seem for the lesion lengths, shows binary restenosis, the angiographic endpoint plotted against vessel diameter over the range of just 2 to 4; I didn't go all the way up to 5 here. Control is the open circles at the top, and Cypher at the bottom. And again we see, at least with this particular endpoint, good separation between the control and Cypher stent, a strong treatment effect--at least, we believe the extrapolation still looks pretty good even to the extremes of the vessel diameters studied.

But again, if you look at the clinical endpoint target vessel failure, as we did before, this looks at target vessel failure plotted against vessel diameter over that same range, and here, I have plotted again the control, and one little feature is that the grade portion of the control indication, control graph, on the left side of the chart indicates the range in which that control stent is really not an approved device. So [inaudible] certainly that comparison is Cypher versus an approved stent.

And we see over much of the range, anyway, there appears to be good separation both in terms of the estimated treatment effect and the confidence in that effect, although as we get up to the upper end, both a few patients and the fact that also the event rates are low, makes it harder, really, to discriminate differences there. These curves are fairly parallel. I did use a quadratic model, I think, and it improved a bit, slightly; linear doesn't really look too much different from this. I did not go all the way up to 5, however, which is one of the proposed stent diameters.

One other feature--there is that sort of dot-dash line right about in the middle of the chart--and although the sponsor didn't make this argument, I'll make it for them--one way of addressing the nonapproval of the control below 3 is to assume that things only get worse with smaller vessel diameters, so that the result at 3 for the control, the lower end of that confidence interval would be an acceptable [inaudible] even for smaller vessel diameters, and if you extrapolate that over, by that argument, you could say that down to 2.5 and even a little below, there is evidence that the Cypher stent is at least as good as the control would be at 3, and that might be viewed as also additional evidence for efficacy.

[Slide.]

The next chart is similar, but I am using again a 7-1/2-month endpoint rather than the 9-month, and as expected, everything is a little bit lower; the event rate are lower. And although there is a statistical separation there, it is a little less clean, and one can't quite as easily make the extrapolation argument for the control below 3.

Finally, let me just recap the safety issue of late malapposition. I think Cordis presented some important data, but let me just review it, because it is one thing we want particularly to get your input on.

This late malapposition, probably better referred to as late-emerging or late-occurring malapposition--we are talking about malapposition that was not necessarily present at baseline, or was not present at baseline, but appears later--we did see malapposition at the angiographic followup in both the RAVEL and SIRIUS studies. In the SIRIUS studies, we know that some of those cases were late-occurring because we have baseline, and RAVEL did not require baseline data, and none was provided to us.

So, there is no apparent clinical correlate with this, and our question would be what might be the implications of this, and has the followup been adequate to address potential implications of it.

Just to recap the extent of the IVUS data and the SIRIUS study, about a quarter of patients were supposed to be getting IVUS--these were done only at selected centers out of the impact study--and followup was not complete to the point where, really, we have baseline and 8-month followup really on only about half of those that were assigned to get IVUS.

[Slide.]

Just to recap, baseline rates were the

same between the control and the Cypher group at about 14-15 percent, but at the 8-month followup, the Cypher rate was 20 percent--again, these aren't exactly the same patients--but the Cypher rate was 20 percent, the control had fallen to 9 percent in the matched-pair analysis. It appeared that among those in the Cypher group, about half of them healed and half of them persisted, but there was an additional cohort that appeared late, so that of the 19 percent or so, about half of them are late-occurring malappositions.

In the control group, again, about half of them healed, but at least in this particular study, there were not late-occurring malappositions.

[Slide.]

And RAVEL, there, everybody was supposed to get angiographic followup, and a subset of centers did the IVUS, and followup was very good there, so I don't have that table for this one. But again, the rate--and this was at 6 months--was around 20 percent for Cypher and 4 percent for control, so fairly similar for followup rates, a little different in the control.

So we really don't have information on how much of it was late-occurring as opposed to persistent from the time of the target procedure.

So, as I mentioned, there are no clinical sequelae, and this is just to recap what the extent of followup is so far, and I think more is available, and I guess that is on its way to us, or we have it now, but we have not had a chance to look at that.

[Slide.]

In the SIRIUS study, followup was at least 9 months, and at this time point, more should be available. The RAVEL study looked at patients for a year. The First-in-Man is an opportunity to look at 2-year followup, but again, the patient numbers there are small. But based on the clinical data, we have seen so far, there is nothing necessarily correlating with the finding of late malapposition.

[Slide.]

This is to recap our clinical conclusions. Overall, we feel there was evidence of safety and effectiveness, but extension to diameters outside of the 2.5 to 3.5 mm range is less definitive. The sponsor would like to use 2.25 up to 5.0.

I should mention that although some patients in the study had diameters well below 2.5, they were all treated with a 2.5 mm stent in this study; nobody used the smaller sizes that are being proposed.

Extension to longer lesions is also less definitive, and for both of these, we have asked the sponsor to analyze these issues, and they have provided some analysis to us.

And finally, the IVUS suggests some abnormal remodeling, but we don't necessarily see any clinical impact at this point.

DR. PONNAPALLI: May name is Murty Ponnapalli. I am a biostatistician in the Division of Biostatistics in CDRH.

[Slide.]

The first slide is on statistical evidence for effectiveness for vessel diameters larger than 3.0 mm. John Hyde already gave the statistical analysis. The control was bare stent. But for vessel diameter less than 3.0 mm, the bare stent is not approved by the FDA, so we ran into a problem, and the FDA agreed that the company, Cordis, could take historical controls instead of concurrent controls.

Because we could not [inaudible] with historical controls, FDA agreed that the sponsor should make a Bayesian analysis, so my talk is going to be about this Bayesian analysis.

[Slide.]

Briefly to recap the design, the treatment is Sirolimus-eluting stent. What I call the substudy population is 370 patients with reference vessel diameter less than 3 mm. The control is balloon angioplasty in three historical studies.

The primary effectiveness variable is major adverse cardio event rate, MACE, at 9 months post-procedure.

I could not see that the definition of MACE is exactly the same in the historical controls also, and I would like to point this out to the sponsor.

The statistical analysis we used is the so-called Bayesian hierarchical model with noninformative priors for the parameters.

[Slide.]

Pre-planned subgroup analysis--sponsor and FDA agreed to the use of Bayesian methods with a historical control, as I already mentioned, in this subgroup.

As I already mentioned, there is no FDA-approved bare stent for lesions less than 3 mm.

The control is balloon angioplasty.

And Bayesian methods were used to combine the three controls in an appropriate way, accounting for variability between studies, and then compare MACE rates using logistic regression.

[Slide.]

The next slide is on the details of the Bayesian statistics.

This is a scientifically valid way of combining prior information and comparing it with current data. The procedure is to assign prior probabilities to parameter values--for example, effects in logistic regression model; update to posterior probabilities after observing the data; then, base inference on the posterior probability distribution of the parameters.

[Slide.]

This slide is of the hierarchical model.

Bayesian methods for comparing the MACE rate in the SIRIUS study with MACE rates in several historical studies; combines information from control studies, taking variability of studies into account; logistic regression of MACE rates using the covariates reference vessel diameter, lesion length, diabetes, left anterior artery disease, gender, minimal lumen diameter. These are the covarietes used in logistic regression.

Assuming that prior studies are a sample from a larger population after covariate adjustment--that is one of the basic assumptions we make using the Bayesian analysis--just as we used randomness in the non-Bayesian method, we use this assumption in the Bayesian method. We used noninformative priors for the parameters.

[Slide.]

In the logistic regression model, we used the covariates: reference vessel diameter, lesion length, diabetes, left anterior artery disease, gender, minimal lumen diameter. That appears as the fourth bullet there.

We assumed that the prior studies are a sample from a larger population. As I already said, we followed the assumptions necessary to make the Bayesian analysis--which one could question, but all Bayesians use this.

We used noninformative priors for the parameters. What this means is that the prior information that we used is not subjective; it is objective.

[Slide.]

So, using all this and using simulations to arrive at procedural probabilities, we get the following results.

The probability of MACE with the treatment is 7.6 percent. The probably of MACE with the three historical studies combined is 24.4 percent. And the next three rows are the probabilities of MACE for each of the historical studies--for Benestent I, it is 33.6 percent; for Benestent II, 24.4 percent; for Stress, 23.2 percent.

[Slide.]

Summary from Bayesian Hierarchical Model.

The probability of MACE with the Cypher product is considerably less than with balloon angioplasty in any one of the historical studies; and posterior probability is 98 percent that the MACE rate is less with Cypher product than with balloon angioplasty. This is the main criterion when we use the Bayesian analysis. This [inaudible] corresponds to P values in non-Bayesian.

[Slide.]

Then, the sponsor performed a sensitivity analysis. Since there is no randomization between the treatment arm and the historical arm, it may be the covariate, which is not balanced between the two, so a sensitivity analysis was performed to examine what the effect of an unmeasured covariate could be.

The sponsor undertook an analysis of the sensitivity to an unmeasured covariate which has an effect on MACE.

The general conclusion, based on simulations and so on, is that unless the confounding is excessive and the confounder has a larger effect on MACE, the probability that the Cypher MACE rate is better than balloon angioplasty remains greater than 92 percent. It no longer is exactly 98 percent, but it remains about 92 percent.

Now, the summary:

Preplanned subgroup analysis--because there was no approved control agreed upon between the FDA and the company.

Prespecified and appropriate Bayesian analysis plan.

Posterior probability is 98 percent that Cypher product MACE rate is better than balloon angioplasty.

Analysis is relatively insensitive to the effects of unmeasured covariates.

Thank you.

DR. LASKEY: Thank you.

MS. FOY: Now, for the record, FDA would like to obtain panel input on the following questions:

Question Number 1, for the evaluation of safety. The safety endpoints evaluated in the SIRIUS study included: MACE to 270 days; stent thrombosis to 30 days; and late thrombosis to 270 days. For the Cypher product, these were 7.1 percent, 0.2 percent, and 0.2 percent, respectively. For the Bare Bx Velocity stent, these same parameters were 8.9 percent, 0.2 percent, and 0.6 percent, respectively.

Do the data submitted on the Cypher product provide adequate assurance of safety?

Question Number 2. The applicant has requested approval for a range of stent diameters and lengths that corresponds to a nominal drug dosage as high as 399 micrograms. The animal studies conducted by the applicant on dosages higher than 180 micrograms were limited to 30-day followup. The SIRIUS study only evaluated 15 subjects who received stents, with a total nominal drug dosage greater than 350 micrograms.

Question 2a. Given the limited preclinical and clinical information outlined previously, please comment on whether there is adequate evidence to support the use of stent diameters and lengths--in other words, 4.5 mm and 5.0 mm diameter with a 33 mm length--with a nominal drug dosage greater than 350 micrographs.

Question 2b. If not, what additional studies or information would be necessary to support the safety of stents with a nominal drug dosage greater than 350 micrograms?

Continuation of Question 2. Additionally, the nominal amount of total polymer ranges from 208 micrograms to 1,184 micrograms for the currently requested range of stent sizes. The animal studies conducted by the applicant on polymer dosages higher than 500 micrograms were limited to 28-day followup. The nominal total polymer amounts tested in the SIRIUS study ranged from 208 to 520 micrograms.

Question 2c. Please comment on whether there is adequate evidence to support the use of stent diameters and lengths--for example, 6-cell and 7-cell stents in lengths of 23, 28, and 33 mm and 9-cell stents in lengths of 18, 23, 28, and 33 mm--with a nominal polymer dosage greater than 520 micrograms.

Question 2d. If not, what additional studies or information would be necessary to support the safety of stents with a nominal polymer dosage greater than 520 micrograms?

Question 3. In the SIRIUS study, the Cypher group had a 19 percent are of incomplete apposition at followup versus 9 percent for the control. This included a 10 percent rate of late incomplete apposition for the Cypher versus 0 percent for the control. In the RAVEL study, the rate of late incomplete apposition was 21 percent versus 4 percent for the control. There was no obvious clinical correlation between late appositions and adverse events.

Question 3a. Please comment on whether additional information is necessary to evaluate the significance of the late stent malapposition found in the clinical studies.

Question 3b. Is there any specific targeted followup, additional clinical investigation, animal studies, and/or bench-testing that should be requested to contribute information that would be important regarding the clinical findings?

Question 4. In the RAVEL study, subjects received ASA for 6 months and clopidogrel or ticlopodine for 2 months. In the SIRIUS study, subjects received ASA for 9 months and clopidogrel or ticlopodine for 3 months. Please discuss your recommendations for the antiplatelet therapy for patients receiving the Cypher product.

Question 5. The potential for interactions with several drugs has been evaluated as described in the Rapamune labeling. Interactions with other drugs might be expected based on known metabolism by Cytochrome P3A4. Please comment on whether the application adequately address drug interactions that are likely to be important or of interest. If not, what other information or studies should be requested?

Question 5b. Has followup been adequate to address concerns about possible systemic adverse drug effects?

Question 6--we are going on to the evaluation of effectiveness now. The primary effectiveness endpoint for the SIRIUS study was target vessel failure at 9 months. Rates of TVF at

270 days were 8.6 percent for the Cypher group and 21 percent for the Bx Velocity control group. Does the evidence presented on the Cypher product provide reasonable assurance of effectiveness at 270 days?

Question 7. Prolonged inflammation and notably increased restenosis were observed when polymer-coated but drug-free stents were implanted in swine. In swine implanted with Cypher product--in other words, coated with both drug and polymer--this effect was not observed at one month post-implant but was observed at both 3 and 6 months post-implant.

Given the nonparallel time lines of healing between juvenile normal pigs and atherosclerotic older patients, do these findings raise significant concerns about the ability of the clinical followup to address the possibility of a similar delayed occurrence of neointimal hyperplasia?

If so, please comment on whether additional testing or followup, either pre- or post-approval, is necessary to support the effectiveness of the Cypher product.

Question 8. The temporal relationship

between scheduled angiography and revascularization, and analysis of the subgroup that did not have angiography, suggest that angiographic outcomes may have influenced the clinical outcomes in a way that differentially affected the control group.

Please comment on the adequacy of the primary endpoint, which is 9-month target vessel failure, for capturing the expected clinical benefit of the Cypher product in light of the possible influence of 8-month angiography results. Are there other ways the clinical impact should be assessed either for (a) evaluation of efficacy in determining the appropriate indication, or (b) for information to be conveyed in labeling?

Question 9. Because the control stent is not approved for de novo stenosis in vessels of diameter less than 3.0 mm, the applicant provided additional analyses, including a Bayesian comparison, to historical angioplasty data.

Please comment on whether adequate evidence has been presented to demonstrate effectiveness for stents with diameters less than 3.0 mm.

Question 10. Univariate regression

analysis of data collected in the SIRIUS study suggest that the treatment effect may be reduced in longer-length lesions. This could be due to either a true diminished treatment effect or a lack of power--for example, too few subjects--to detect a treatment difference in subjects with longer lesions.

The applicant has performed logistic regression analyses, but these analyses only included main effects and did not specifically evaluate the possible interaction between each variable--in this case, lesion length--and the treatment effect--for example, an analysis of treatment effect by covariate interaction.

Question 10a. Does the data presented provide reasonable assurance of effectiveness for the treatment of the full requested range of lesion lengths--less than or equal to 30 mm?

Question 10b. The protocol for the SIRIUS study specified the inclusion of subjects with reference vessel diameters from 2.5 to 3.5 mm. The proposed indications for use include reference vessel diameters of 2.25 mm as well. Does the data presented provide reasonable assurance of effectiveness for vessel diameters of 2.25 mm?

Question 11, which relates to product labeling. One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse effects or events with the use of the product, and explain how the product should be used to maximize benefits and minimize adverse effects.

Please address the following questions regarding the product labeling.

Question 11a. Please comment on whether the Indications for Use Statement identifies the appropriate patient populations for treatment with this product. Specifically, subgroup question 1, has the application provided reasonable assurance of safety and efficacy for treating the full requested range of vessel diameters--2.25 mm to 5.0 mm. If not the full requested range, what range of vessel diameters should be included?

Subgroup question 2. What length of lesions should be included in the Indications for Use?

Question 11b. Please comment on the contraindications as to whether there are conditions under which the product should not be used because the risk of use clearly outweighs any possible benefit.

Question 11c. Please comment on the Warnings/Precautions sections as to whether they adequately describe how the product should be used to maximize benefits and minimize adverse events.

Specifically, please comment on whether a warning or precaution related to subsequent brachytherapy should be included in this section.

Question 11d. Please comment on the Operator's Instructions as to whether it adequately describes how the product should be used to maximize benefits and minimize adverse events.

Question 11e. Please comment on what aspects of drug pharmacology, mechanism of action, pharmacokinetics, drug interactions, or systemic effects should be added to the labeling to maximize benefits and minimize adverse events.

Question 11f. Please comment on the remainder of the product labeling as to whether it adequately describes how the product should be used to maximize benefits and minimize adverse events.

And lastly, post-market evaluation.

Question 12. The Panel Package included the available 9-month data for the Cypher product in the SIRIUS study. In addition, the available 12-month data were provided from the RAVEL study, and the available 18- to 24-month data from the First-in-Man feasibility study were provided.

The applicant has proposed continued followup, out to 5 years, on subjects from the SIRIUS, RAVEL, and the First-in-Man studies.

The applicant has also proposed to collect data through one year on approximately 1,000 to 2,000 patients implanted with the marketed product using an electronic database.

Question 12a. Please discuss long-term adverse effects that may be associated with implantation of the Cypher product including late thrombosis formation, aneurysm formation, myocardial infarction, and late stent malapposition.

Question 12b. Based on the clinical data provided in the Panel Package, do you believe that additional followup as proposed by the applicant is appropriate to evaluate the chronic effects of the implantation of the Cypher product?

If not, what additional followup information should be collected? Specifically, how long should patients be followed, and what endpoints and adverse events should be measured.

That's the end.

Committee Discussion

DR. LASKEY: Thank you, FDA.

I am going to arrogate my Chairman's prerogative here and move on beyond the panel asking questions of the FDA. I think we can do that a little later on. Let's get to the crux of the issue.

I would like to open the committee discussion by asking Dr. Krucoff to provide us his review.

Mitch?

DR. KRUCOFF: I'm going to have some questions along the way, so is it fair to just call people up as we need them?

DR. LASKEY: Actually, at this point, it would be appropriate to ask the sponsor to please step forward; it may even be a shade cooler toward the front of the room.

We are cognizant of this problem, and we have been working on it for the last 2 hours.

Thank you.

DR. KRUCOFF: I have to start with at least a couple of perspective comments, and if I am wrong in these perspectives, that will change a lot, so I'll just rely on somebody to jump in.

As an interventionist and with so much awareness of the obvious effectiveness of what is a breakthrough and a major source of human misery for all of us in this technology arena, I think I can only say that I share a lot of the excitement that has brought this product clearly to an expedited review on an accelerated pace.

It does, though, leave me with a sense of to be cautious about the mandate to today's review committee to review a clinical trial based on the data that we have at hand. Years ago, Bill Roberts taught me that a medical device is essentially the replacement of one disease with another--hopefully, a less severe one. And I think we have to be cognizant of that.

I want to thank the sponsor and their colleagues from the HCRI for putting together an enormous amount of data in a very clear, concise way, both what I got in the panel pack and in the presentation today.

I also want to thank the FDA team, from across sectors of the agency, on a combined drug device for also putting together a panel pack that

I felt was extremely helpful in synopsizing that.

So what I am left with are a few assumptions. One assumption is that as the first panel pack I have ever received with an incomplete Letter of Major Deficiencies, that is not our business today; that follow-through on the manufacturing elements and essentially the completion of those deficiencies is going to happen through a separate interaction. So I am going to step away from that, other than the fact that, obviously, the ability to manufacture a stent that delivers in clinical practice what has been delivered in a pivotal trial is part of the assumption that I am going to move forward into the data with.

The other part of this, though, that is clinical data-oriented is that I simply am not a believer that the practice of the black art of data manipulation constitutes a replacement for data, and that ultimately, if we are going to subject human beings to an intervention that we don't understand very well, the least we can do is start where we have data and then move conservatively as data has accrued rather than trying to use analyses that are so complex that even a statistician doing the analysis cannot honestly tell us whether it is a lack of numbers or a change in effectiveness that we are looking at when we look at charts and graphs.

The last assumption that I'm going to go through this with is the assumption of a clinician, that ultimately, the questions and answers here of where this device matters most is in how it is likely to be used.

So my first question, actually, to the sponsor is: What is the total dose of drug delivered when 9-1/2, or let's say 10, stents on an average of 12 mm in length are all put into a single human being in a live course overseas in front of about 200 interventional cardiologists? What is the total dose of drug in that individual?

I think the average we got on pencil and pad was about 15, or 10-15-ish.

DR. DONOHOE: About 1,500 micrographs.

DR. KRUCOFF: Okay. And I didn't hear anybody use that figure this morning. I just think we have to be realistic when we think about this as a breakthrough that clearly is going to help literally millions of people who suffer from coronary artery disease, that as it gets out into real clinical practice, if we have fuzzy edges here, they are going to get a lot more fuzzy in clinical practice, and that is the spirit that I'm going to start with looking at the data, with where we really have data, and you clearly have data that is solid and real and to me provides a starting point.

My ignorance--can you help me--in the device design, when you actually spray drug, does the drug only adhere to the outer surface, or is it also on the interluminal surface of the stent scaffolding.

DR. DONOHOE: The polymer in the drug distribution is both in the outside and the inside of the stent, evenly distributed.

DR. KRUCOFF: Okay. And is there any model--because I couldn't find any--as to if it is evenly distributed--is 50/50 a fair assumption--so about 50 percent of the total drug on a given length of stent would be opposed directly against the outer surface, whereas the other 50 percent would be what, actually, the bloodstream was seeing?

DR. DONOHOE: Yes, I think that's correct.

DR. KRUCOFF: Okay. The second question I have around the study itself was in the inclusion and exclusion criteria, and Rick, I'm going to ask you or Dr. Potma maybe to help me with what, if any, analyses have been done on visual sight readings in the kinds of breakdowns we have looked at, as opposed to my assumption, which is everything that I could tell in the pack or in your slides today are from the core lab, which of course is understandable.

The reason I ask, though, is that the inclusion criteria, length of lesion, in this study was from 15 to 30, whereas the average length of a lesion coming from the QCA lab was 14.4. So the average lesion length is actually below the inclusion criteria overall. And I am going to assume, but I would actually like to ask, is that just the difference between sight readings, visual readings, and estimates of lesion length and the QCA?

DR. POTMA: My name is Jeff Potma. I was the director of the angiograph core laboratory for this trial.

My disclosures are that I have no immediate stock equities in the company. I do serve on the advisory board, and the compensation of that is under the Harvard clinical research guidelines for compensation.

That's a good question, because we noted from the first time we did quantitative analysis that our assessment in the core laboratory is quite different than the investigator's assessment who is standing at the table.

To describe the discrepancy, it requires that we understand that the quantitative algorithms begin to call a lesion length when there is a 20 percent lumenal narrowing. It is just how both the CAS-2 [phonetic] system and the CMS system that we use begin to do that. And it needs to be a consistent drop in the lumen diameter, and that continues until the vessel then becomes near 20 percent of what it normally is on the distal side.

And specifically, then, we just call the single lesion when it is more than 20 percent narrowing.

Now, there is a discrepancy, because in the catheterization laboratory, oftentimes, an investigator will choose a stent length based on where he or she sees lumenal irregularities within the vessel, and oftentimes those lumenal irregularities do not qualify for our greater-than-20 percent lumen [inaudible] by the angiographic core lab. So both with the RAVEL trial as well as with the SIRIUS trial, our lesion lengths were shorter.

We used that 20 percent because that provides us the greatest reproducibility for repeated measurements. And that is very important for us in the core laboratory to make certain that our lesions are reproducible. The quantitative algorithms were set up to be reproducible, and that is the discrepancy.

To specifically speak to the SIRIUS trial, I reviewed all the procedural angiographs myself throughout the beginning course of the trial, and whenever there was a clear discrepancy, when there was clearly a discrete lesion, I would write back to the investigator and say this lesion is too short for this study; please include a longer lesion length. And I do believe that that did have some influence on our lesion length throughout the course of the trial.

So the answer to your question is there is a discrepancy. It is a discrepancy because our quantitative angiographic algorithms aim themselves at reproducibility, and the clinicians want to make certain they treat all areas of lumenal irregularity within the vessel, which is why they are visually seeing a longer lesion length that we are measuring in the quantitative core laboratory.

DR. KRUCOFF: All right. And Dr. Potma, while you are there, let me just extrapolate, then--what I think was mentioned during the presentations, the difference in diameter of the reference vessels between visual and a smaller diameter which came out of the QCA lab presumably is also a function of just a quantitative algorithm versus a visual estimate.

DR. POTMA: That is correct, and we have looked at that quantitatively in a number of different studies, including the new approaches to [inaudible] ventral registry, which was subsequently published. I think that Dr. White's discrepancy is about 10 percent difference is what we see, about 0.3 millimeters.

So we do feel that the majority of patients fit the inclusion criteria of the trial. Our QCA readings typically come out to be 0.3 millimeters smaller than the visual estimates.

DR. KRUCOFF: Thanks, Jeff.

So, understanding that--and I think we all understand the difference here, that in clinical practice, nobody is going to be sending their films to a QCA lab before they pull a stent off the shelf--I would have loved to see some of the breakdowns, since lesion length and vessel diameter are clearly important issues of where this stent is going to optimally have its impact.

But some of these analyses based on sight estimates, just to see whether that actually changes any of the conclusions around where its efficacy is or isn't in longer lesions/smaller vessels and larger vessels/shorter lesions would have been of interest to me just as a reflection of what is more likely to happen in clinical practice.

You guys set an inclusion criterion of greater than 15 on the lower side. Was there a rationale for not wanting shorter lesions?

DR. KUNTZ: Yes, there was. This study was aimed at showing a benefit clinically in restenosis. And as you know from the large amount of stent studies that were done in the 1990s, restenosis rates were anywhere between 9 or 10 percent--it depends on the case mix--to about 16 or 17 percent clinically.

So in order to have adequate power with a reasonable sample size to demonstrate a benefit, and also to focus on patients who probably would benefit the most from a drug-eluting stent, those at highest risk, we aimed to try to enrich the population of patients at risk.

The lesion length is everything, because once you start to enroll patients with a window to the right of larger lesion length, you also include a higher frequency of diabetic patients, and then the two are actually synergic in producing a restenosis rate.

So when we do our calculations, we see modest increase in mean lesion length, from 10 to 11 mm in the stent studies to approximately 14.5 in this study, but that also increases the proportion of diabetics by 50 to 60 percent. And as you can see, the control rates of restenosis went from this study, studies in simple lesions, the stent, the Bx velocity of approximately high teens, to 36 percent.

So we actually did meet our goal, which was to get a population that was at risk for restenosis so we could have adequate power to demonstrate a clinical benefit, and that was the main reason for making the window 15 to 30.

We also know that when you tell clinicians to give us 10 to 20 mm, they give us about 11; but when we said 15 to 30, we thought they would give us hopefully 15, and they gave us 14.5. That was the other reason.

DR. KRUCOFF: So was there a rationale, then, in the pursuit of the labeling, the actual driver that will bring this to market and clinical use, for proposing a labeling that does not stop at a short length? I mean, if the rationale is that there is a lower incidence of vulnerability in short length--say you want to design a trial where you will be able to demonstrate effectiveness, et cetera, et cetera--why would you propose labeling that includes a shorter length where patients do relatively well with standard bare metal stent?

DR. KUNTZ: That's an excellent question, and other than the fact that we do have a fairly decent subset of individuals who have lesions less than 14 mm that can be treated with shorter stents, and the benefit was still preserved--I think I'll hand it over to Dennis to answer. That's a good question.

DR. DONOHOE: I think, actually, the way we viewed it was the lesion length data generated in RAVEL combined with SIRIUS, which was providing data on a fuller spread of lesion lengths, from shorter to longer, and the request for shorter lengths, that is, less than an 18 mm stent, or specifically, 13 to 18, we assumed that the data generated in RAVEL in combination with SIRIUS would be adequate to demonstrate that there was still additional therapeutic benefit in treating those shorter lesions compared to a bare stent application.

DR. KUNTZ: I think one other thing to keep in mind is that--and again, I'm not speaking for the sponsor here, but just as a clinician looking at the data--the 8 mm stent may not be intended primarily to be a stent to be placed for primary lesions, but it is often a lesion to be used to tack up a dissection and so on. So availability of a short lesion when using an appropriate long stent--a short stent, I mean--is actually quite beneficial if you don't want to add a lot of stent to the times when you need to have a second stent used.

DR. KRUCOFF: I'm not sure of the availability of a short stent and labeling for short lesion are necessarily one and the same, though.

Okay. Again, my understanding of what I saw in the panel pack and what was presented today was that we saw essentially an actual treatment array of analyses rather than an intention to treat array of analyses, that the deregistered patients and the couple of patients who were treated with the wrong stent during the course of the trial were placed in there.

Is that correct, or is that not correct?

DR. KUNTZ: Let me clarify the deregistered patients, because it seems like it is a special case in this trial, but it actually happens in every trial.

When you get a random assignment, we try to minimize the distance between the random assignment and the actual application of the random treatment. In some studies, like bypass surgery, where you have to actually set up the surgical treatment--a bypass, if you are looking at a variety of bypass machines, for example--the final arbitrator of the eligibility isn't available until the patient actually gets operated on, but they have to get the random assignment before to get consent and also to have the equipment set up. So oftentimes, you get situations where you can't actually apply the device because the last arbitrator of what you do to get into the trial isn't known.

Many times in this study, although we tried to minimize as much as possible, there were a few operators who had outside films that demonstrated the lesion, and before they brought them into the lab, before the patient was dosed with a hypnotic or a sedative to get consent, they actually randomized them.

We tried to caution against that in as many cases as we could, but often those patients were found not to have lesions and therefore were not treated at all.

So most of these patients were not eligible because they didn't have lesions. That was the majority of them. This was a blinded study, and we know the blinding part we think worked very well up front. If there was any issue of blinding, it was in the followup part. So it wasn't surprising to us that this frequency of these registrations is equally distributed, because nobody knew, for example, that they were going to deregister a patient because they thought they were going to get the SIRIUS stent for the control; it was evenly distributed between the two arms.

So it was a low frequency. They never got treated, anyway. There was no treatment for us to follow in those patients. So this isn't the classification of clinical trials called "withdrawal" where you actually shift [inaudible] patients who withdraw from the study; it is patients who never actually received the treatment at all.

DR. KRUCOFF: Okay, I'm with you there. I guess what I'm trying to get at--because there are at least two places in the panel pack where this is referred to--is that we are really not looking at an intention-to-treat analysis. Is that wrong?

DR. KUNTZ: We could do the intention-to-treat analysis. The problem is that they don't have restenosis; they are not eligible to have restenosis because they never got treated. Many of these patients never got therapy. Some did get treatments per se, but many of them didn't get treatment at all. They were on the table found not to have a lesion.

So in order to understand freedom from repeat revascularization, they [inaudible] the first one to have the repeat from. If we were to add in there followup at some event, at 9 months, we would probably be looking at atherosclerosis progression in most of those cases, and they would be equal to our non-TVR rates, and we would be adding 4 percent times 2 percent to both arms.

It is certainly possible to do that, but unfortunately, we didn't engage the clinical followup in those patients because they never got the assigned therapy.

DR. KRUCOFF: Okay. Rick, in the length and diameter and the 16-cell breakouts that you shared with us today, is that amongst the non-FDA-reviewed data--whatever--

DR. KUNTZ: Yes, it is.

DR. KRUCOFF: The paper by Dr. Ho--and you were in the senior author, I think--in the 1998 Circulation that you started with actually was 32 cells, not 16 cells.

DR. KUNTZ: Right.

DR. KRUCOFF: And you had broken them out in 5 mm increments and vessel sizes up to 4.0, discretely, presumably because you had the numbers in your dataset to make that a sensible thing to do.

As I look at your presentations, though, here, the 16 cells essentially ought to have been collapsed as everything 3.0 and greater from a diameter point of view; so 3.0, 3.5, 4.0.

DR. KUNTZ: Actually, we broke them into the actual terciles. It was actually 2.5 to 3.0, 3.0 to 3.5, and 3.5 and greater. We broke it into where the data was [inaudible]--less than 2.5, 2.5 and 3.0, and greater than 3.0.

DR. KRUCOFF: Greater than 3.0.

DR. KUNTZ: And those were the actual terciles of the dataset. And we did that because in the article by Dr. Ho, we actually had 8,000 patients to draw upon, and so this had 1,000, and so the 9 cells we have times 2--because [inaudible] which is 18--just made sense because we had fewer datapoints.

DR. KRUCOFF: Yes, but--and again, I think it is simply a factor of not having the numbers--but the areas that clearly we would expect to be most illuminating from that kind of breakout would be the areas either where bare stents would do best, so you would see at least treatment effect just because you don't have much of a target to reduce, which would be in the larger/shorter lesions, the upper lefthand, and I guess in collapsing that into 16 cells as opposed to the 32, I am left, really, with a question mark, and I think the answer to the question mark is that you probably just don't have enough numbers.

DR. KUNTZ: Actually, in the initial analysis that you referred to earlier, there were three columns and four rows, so we had 12 time 2 is 24. The only thing we added was we had data of 3.5 to 4.0, and we don't have those cells in here because the study was intentionally 3.5, even though there were a fair amount above that. We actually divided them into the terciles. So we [inaudible] just one row. That's the major shift. So there was no collapsing of the lesion lengths part.

So they are almost spot-on with respect to the same kinds of results in patients that--and we do see in fact a lot of patients who have low risk and a lot of patients who have high risk.

DR. KRUCOFF: So you feel from that breakout that you have enough information to feel comfortable that vessels of diameter larger than 3.5 mm--4.0, 4.5, 5.0--that there is data from this pivotal trial to support an indication here?

DR. KUNTZ: I feel comfortable that the data supports the recommendation up to 4.0 mm. I think there is very little data above 4.0 to 5.0, other than the fact that one would expect this to continue above 5.0 is the logical extrapolation, but there is not data to support that. It is supported--we looked at the reference vessel diameters in the datasets, and we do have data that goes up to 4.0 mm in the graph that I showed.

DR. KRUCOFF: Okay. And again, that's all based on QCA measures?

DR. KUNTZ: That's correct.

DR. KRUCOFF: You didn't share any data with regard to IIbIIIa's other than from, what I saw, a significant proportion of this population was treated with IIbIIIa's. Have you looked at interactive effects or any sort of small vessel/large vessel, short lesion/long lesion--

DR. KUNTZ: We did extensive analysis of the IIbIIIa inhibitors with respect to interactions also to see if there was a main effect of restenosis, and so far, we couldn't find that there was any effect on restenosis with the IIbIIIa inhibitor on acute complications or any other interaction. But again, it's not really fair for us to make those inferences about IIbIIIa inhibitors because they were selected by the operators; they were not randomized.

So inasmuch as we can observe based on the individuals, we can't see that we saw any synergistic effects. Often in studies like this, especially those at risk, the IIbIIIa inhibitor subsets come out with actually worse rates, but that's unfair to the IIbIIIa inhibitors, because physicians tend to use those inhibitors for patients they feel are at highest risk, so it tends to be highly confounded by the perceptions up front.

So I think the most important analysis of a IIbIIIa inhibitor in a trial like this is to make sure we don't see anything funny happening or anything where there might be some negative synergism which we didn't observe. It is hard for us to make any inference about the effect of IIbIIIa inhibitors on the study design.

DR. KRUCOFF: Okay. Thank you.

Can you help me--in a patient denominator of about 1,000 patients--and I am going to just pick out late incomplete apposition rate for a second--so, say 10 percent have late incomplete apposition. And let's say one of those 10 actually turned into ultimately a clinical problem. At what level, from a safety analysis standpoint, is the Beta error in a 1,000-patient denominator? Where do we start to miss a one percent complication rate?

DR. KUNTZ: Well, I may have somebody else talk about the late apposition issues per se, but statistically, I can offer some kind of off-the-cuff--

DR. KRUCOFF: Yes, that's really what I'm asking.

DR. KUNTZ: If we assume that when you manifest an outcome from late apposition such as spontaneous dissection, perforation, or symptoms leading to angiography discovery, discovery of aneurysm, certainly in our almost one year or more followup on these patients, we have not seen that yet in a patient, especially those identified in the small subset of IVUS or those who we did have an opportunity to do IVUS in.

So, I don't have the calculator with me, but you would take PQ over N-squared and come up with 9.6, and that gives you the confidence analysis for that estimate, and my guess is--

DR. KRUCOFF: You can't do that in your head?

[Laughter.]

DR. KUNTZ: [Inaudible] but I think that we probably have fairly tight confidence that the incidence of this event occurring is probably less than half a percent if it is a problem from the [inaudible].

DR. KRUCOFF: Do you know the average--

DR. BAILEY: Take 3 over the denominator--that's roughly your upper confidence limit? You had no events out of how many malappositions?

DR. KUNTZ: Well, we had 10 percent rate of malappositions, so you would take 10 percent times 500 randomized.

DR. BAILEY: So how many malappositions were there--30?

DR. KUNTZ: It's 10 percent of the small subset; it will be extrapolated from the whole group--

DR. BAILEY: How many malappositions were there--about 30?

DR. DONOHOE: Seven patients with [inaudible] apposition.

DR. BAILEY: Seven.

DR. KUNTZ: Seven, but we had a small subset [inaudible] ultrasound.

DR. BAILEY: Okay. So your upper confidence would be 3 over 7--actually, it's less than that--probably 2 over 7.

DR. KUNTZ: We had a small sample of approximately 150 patients who had [inaudible] available. In that, there were 7 assigned to the [inaudible] for Sirolimus, and that calculated out to a 10 percent rate [inaudible]. So [inaudible] late apposition was 10 percent in the sample. Presumably [inaudible], then, that would be 10 percent of 500 patients. But we would expect that 50 patients would possibly have a late apposition, okay?

DR. BAILEY: Okay. Maybe I missed the point, but I think the question was what evidence do you have that late apposition is benign.

DR. KRUCOFF: Let me--because I was actually asking the statistical question for a purpose, not to pick on late apposition in discussion at this point. What I'm really thinking about is if these stents are placed in one million human beings per year, and we are making this decision on safety data based from a 1,000-patient study, which is normal at one level, on the other hand, this really is a breakthrough technology. So what I am really asking is if we missed a one percent or a one-in-1,000 complication of any sort, where is the cutoff? Where is the beta error level for a 1,000-patient denominator?

DR. KUNTZ: And my answer to that is that if we assume that a clinical manifestation of that late apposition is something like an aneurysm or something that leads to discovery of a dissection, which we didn't observe, then, what we observed was zero out of potentially 50 cases that would have had that rate.

So given a late apposition, the confidence interval will be 2 percent plus or minus some variable, and that would be PQ over N, whatever that is, probably plus or minus two or three percentage points, for patients who have late appositions.

For any patient treated, it would be the estimate of zero over 500 patients. So it all depends on whether we classify them as having the arbitrary finding at IVUS of late apposition versus any patient who gets treated.

So in all cases, the lack of any significant consequence obviously is good, but if we want to be precise and say that we had confidence that there was less than a one percent rate of individuals who would be identified to have late apposition, we don't have that power.

DR. KRUCOFF: Okay. Because obviously, one of the questions that we are going to address for the FDA questions is what is enough surveillance of the population who have already been implanted. So we'll have to come back to that at some level.

Do you have the average number of stents placed per patient in the SIRIUS population.

DR. DONOHOE: There were on average 1.4 stents placed per patient.

DR. KRUCOFF: So, 1.4--and that's just about what CSM averaged when they created a reimbursement code for this. So this should be a reasonable representation, ultimately going forward, if clinical practice and the reimbursement projections are anywhere close to one another--which they probably won't be. Okay.

Let me just shift into the last array. I found myself at the end of all of this--and if we need somebody from Wyeth, maybe we could ask them to come up to the table--but one of the things that I was impressed by--and whether it is because half of the drug is opposed directly to the outer component of the stent and really doesn't get into the bloodstream--is the low blood levels that are associated with this entity. But I found myself wondering about allergy rather than other types of toxicities. And as I went through the Rapamune data, for instance, in what was reported in patients who are all on steroids and transplant scenarios was about a 5 percent incidence of skin rash determined to be allergic.

So I have two questions. One is whether this is understood to be an idiosyncratic or a dose-related type of skin rash, or whether allergies to the drug in general have been appreciated to be idiosyncratic or dose-related. That's one question. And the second question is going to be did you observe any allergic reactions?

DR. SCEROLA: Joe Scelora [phonetic] from Wyeth.

We consistently observed a higher rate of a nonspecific rash in patients treated with Sirolimus, which generally disappears despite them continuing on the drug. So we don't think it is truly an allergic reaction; we think it is some other adverse effect.

In our clinical trials, we actually saw a few clearly-documented cases of hypersensitivity reactions--in part, as you noted, these patients are also on steroids, cyclosporin, for the approved indications.

In our post-marketing reports from the field, which frequently come not well-documented, there have been some other cases of reported allergic events with the drug, but we don't have enough data to say that it is dose-related, and we don't really have enough data to say that there is truly an idiosyncratic reaction to it.

DR. KRUCOFF: Okay. And the second question was in the SIRIUS cohort who received drug stent, and combining from First-in-Man through RAVEL, have you all encountered an allergic reaction?

DR. DONOHOE: We have looked at that specifically, and actually--there is a slide that we will put up shortly--we have looked at the incidence of allergic reaction. That assessment was based on the investigators' assessment that there was an allergic reaction.

[Slide.]

As you'll see in this slide, this is the total reported number of allergic reactions within the first 30-day period following the index procedure, and you'll see in terms of the absolute number of patients it is almost equal in both treatment groups. And we have also broken out or identified factors that seemed to be contributing to the allergy.

The medication line, which accounts for most of them, was either medication given during the intervention procedure, and the bulk of those outside the procedure was actually the antiplatelet therapy.

DR. KRUCOFF: Okay. In some of the animal reports and followup, there was a description of a possible delumenation local calcification. I have heard none of that observed either, or seen any of that observed in the IVUS population in humans at 9 months. Have you all come across any sort of calcification or other unusual observations?

Peter?

DR. FITZGERALD: My name is Peter Fitzgerald. I am an interventionalist at Stanford.

I run the core cardiovascular analysis laboratory there. I have by way of disclosure no financial interest in Johnson and Johnson. I am a participant in the core lab facilities and am under the guidelines of Stanford's conflict of interest regulatory bylaws.

With respect to the IVUS and being able to look at patients who have had these implants both in the bare metal population and the drug-eluting population, we have seen no change in placque composition. For example, that would be fibrous placque turning into calcific placque, either behind the stent struts, where potentially the highest dose can be delivered to the endovasculature, or at the edges, the proximal or distal reference segments.

As far as the delumenation issue, that is a tricky one to be able to assess by intravascular ultrasound. The axial resolution of a typical 30- or 40-megahertz intravascular ultrasound catheter is on the order of 150 microns, which well exceeds the average thickness of the combination of the polymer and drug.

DR. KRUCOFF: So, Peter, would it be fair to say that--and understanding the animal models have different time frames--but roughly in a time frame in the human that would probably at least incorporate the time frame of these observations in an animal, you haven't seen any unusual evidence of calcification or change in composition of the lesions?

DR. FITZGERALD: Not at all, not only in this study but several other approaches both inside and outside the United States.

DR. KRUCOFF: Okay, thanks.

A question for one of your interventional experts, I guess--it's speculation, but again, it's my interest, and I think we may touch back on part of this.

For the small percentage of patients who get drug-coated stents who do have instant restenosis, what would the next line of treatment be?

DR. MOSES: I am Jeffrey Moses, and I'm an interventional cardiologist in New York. I do some consulting work for Cordis, and they did pay for my trip here, and I have some stock in my retirement fund.

I think one thing to understanding is the nature of restenosis; even though we categorize them similarly, it is a totally different animal in the failure mode here. It is predominantly marginal, and it is almost exclusively focal. Diffuse stent restenosis is a very, very rare event with us.

So if it is marginal, it will probably be treated with another stent, probably another drug-eluting stent. I think the diffuse, if we do encounter it, we'll treat conservatively with standard techniques.

DR. KRUCOFF: Brachytherapy?

DR. MOSES: At this point, I don't think we have any evidence to assume that brachytherapy has any either safety or efficacy given the fact that we have already manipulated the molecular environment in that vessel. And personally, I would not recommend it at this time, until we have further evidence.

DR. KRUCOFF: Would you caution against it?

DR. MOSES: Until we have evidence, I would not recommend it.

DR. KRUCOFF: Okay. Well, that actually brings me to my last question, which is why, in Section 3.2 of this panel pack under "Patient

Labeling," you have a long discussion about the checkmate system.

DR. DONOHOE: I think that's actually a packet to the patient, just explaining what the options are in general for treatment. It's consumer labeling.

DR. KRUCOFF: Right after "What Happens After Your Angioplasty or Stent."

DR. DONOHOE: Yes. That's entitled, "A Guide for Patients."

DR. KRUCOFF: This is the patient guide; right?

DR. DONOHOE: Right.

DR. KRUCOFF: Where you start this whole thing about checkmate. So is this actually entitled just as a general, all-purpose--

DR. DONOHOE: That summary--actually, I don't think it makes a statement about recommending brachytherapy after a Sirolimus-eluting stent takes place. I think it is purely reviewing all the potential options the patient could have for treating restenosis or treating stenosis.

DR. KRUCOFF: Okay, thank you.

DR. LASKEY: Dr. White, please.

DR. WHITE: Thank you, Dr. Laskey.

I will be brief only because I think Mitch did such a good job of covering the waterfront, and I have only a few specific things that are more information, I think, than criticism, because I also believe that this is, as an interventionalist, something that I think we have all been waiting for.

One of the issues I have for you is that your recommendations again don't correlate so closely with the data that you provided, so I would like to just probe a little bit at the edges of the dosimetry.

Rick, the table you showed this morning of the proposed Sirolimus-eluting matrix and drug content, where you had on the Y-axis the stent diameters going from small to big, and on the Y-axis, you have the length of the stents and the proposed dosages that would be administered--it is on page 3 of the slides that you handed out at the bottom right-hand corner.

DR. DONOHOE: Are you talking about the drug matrix slide?

DR. WHITE: "Proposed Sirolimus-Eluting Matrix and Drug Content."

DR. DONOHOE: Yes.

DR. WHITE: The only reason I want you to look at that is do you have evidence of efficacy for an 8 mm stent at--obviously, you don't at 2.25--but do you have any comfortability that if I put an 8 mm stent in somebody, a 2.25-by-8 mm stent, that that level of drug at 71 micrograms would be an effective dose level? What supports that theory?

DR. KUNTZ: If we--a lot of--let me just make a couple of opening statements, because there are a lot of issues raised about the modeling of this data.

The parameters for this study were 15 to 30 millimeters in general, and we know [inaudible] go outside those boundaries typically in many trials; and also, 2.5 to 3.5, we know that they stretch out a bit a as well. That's typical. For any randomized trial, we define the reference population, and we do a randomized trial and see who wins.

Then, our inference about the final overall results are made to the reference population that we aimed at [inaudible] criteria. That is typical for a randomized trial.

In trying to figure out where in that

sample zone we aimed at we may or may not have strengths or weaknesses, we probe, and the logical way to probe is to take dimensions that actually affect the outcome, like lesion length and vessel size and so on.

So that is why we do this modeling. And if you actually take the raw data and look at them like we did, you have random chances to move around, so you try to fit a smooth relationship assuming that in biology, the effects are monotonic--that is, they are usually first-order relationships. That is what most biological systems have; that is why fit main effect models.

So the traditional main effect model that we fit here that produced these matrices is based on just conventional analysis of predictors, and when we do that, we see that that cell of the short lesion still has about a 70 percent treatment effect, but the risk of that group, that zone, is actually small to begin with.

So our model suggests that the linearity of the relationship of the predictor and some patients we have in that zone, by looking at the actual raw estimates, are consistent with treatment effect extending to small and short lesions. But that is in a zone where the patients may not have that much risk to begin with--but it is still a profound 60 or 70 percent treatment effect.

DR. WHITE: I guess what I'm asking is--is there data that you have efficacy at that dose level?

DR. KUNTZ: Well, the question is--

DR. WHITE: I understand the model and the--that's good--but could somebody get an 8 mm, 2.5 stent that--

DR. KUNTZ: The problem is that when you look at small subsets, what do you mean when you say is there data? Do you want significant difference, or do you want just the estimate to be consistent with what the overall main effect is--because again, we are looking at endpoints. The overall study is the only one--the overall sample size is used to power one single comparison. So when we get to the areas that have fewer patients representative, usually, what you want to do is show that the estimates are still consistent in the same zone, and we do have data for that. They are consistent. But to actually ask if that small sliver of data provides P values of 0.05 or less--it's in a very unpowered zone.

DR. WHITE: And then, you would make the same argument at the upper end, where you get above the sizes that were actually tested to 4.5 and 5.0 mm stents?

DR. KUNTZ: Yes, and I think the notion is that we know that in general--and again, this gets to--and I don't want to bore you with the modeling part--but it gets to the point of understanding what it means to look at risk. And most risks in general for biological systems in clinical trials are linear, that is, when you look at the data that moves up and down, as our estimates did in the graphs that I showed you, usually, that's because that is an underlying linear effect. So when you fit the model to show that the slope is different at zero, you are suggesting that there is a relationship between this covariate and the outcome. When we look at those data, the separations tend to be very consistent across those zones.

You can also use curvilinear models to fit them, but the curvilinear models have the problem that they might be more dependent on the formula that draws the curve rather than the data that fits it. So there are always controversies about which one to use, and we tend to try to use the linear models whenever we can, unless we can demonstrate that the fit or the quadratic and cubic terms have significance to actually displace a common sense linear model, and we didn't see that. So in our models, what we saw was that the relationships across these zones, especially from around 2.5 to 4.0, had the same level of separation in general if we look at consistent findings that have fit pretty well. And when we tested to see if that was something that was just a model relationship, we actually looked at the raw data, and we saw these points, from 2.5 up to 4.0 mm, for example, still showed relatively low separation as the actual individual estimates as well, which is consistent with the data being consistent with the overall treatment effect.

That's the best way for us to actually make those statements. To get any more specific about saying is there really good evidence to show that we can expect a consistent statistical difference in a patient with really short lesions, we don't have the solid independent data, because the study would have to be focused on those per se. But is the data consistent with those groups of patients having benefit--yes, it is.

DR. WHITE: Do you have reason to suspect that endothelization of these stents is affected by this drug? Is it delayed over what you would expect for a bare metal stent?

DR. DONOHOE: No. The preclinical data we have indicates that re-endothelization is already taking pace by the 14-day assessment and is near complete and is complete by a 30-day period of time. So the preclinical model suggests that there is no delay in re-endothelization, and on a clinical basis, just looking at the thrombosis rates that we see in both acute and late, there is no suggestion that we are affecting significantly delaying or altering the endothelial function.

DR. WHITE: Why did you use a prolonged dose of Plivex or Tyflid [phonetic] in these patients?

DR. DONOHOE: We actually conducted all studies outside the U.S. using 2 months of antiplatelet therapy, and the first studies were conducted in First-in-Man or RAVEL. We picked 2 months because the animal data, preclinical data, suggested that one month was a sufficient term for re-endothelization. Given that we had no clinical data, we opted to add an extra month just as a caution. When we--

DR. WHITE: Because you were fearful about endothelialization being delayed, or--

DR. DONOHOE: No, no. It was just given that we had no clinical data to that point, we had no data to say that 2 months was required, but we felt that providing an extra month was just an extra margin of safety for patients at that point.

DR. WHITE: And SIRIUS went up to 3 months; right?

DR. DONOHOE: SIRIUS was 3 months, yes.

DR. WHITE: Why did you add the month when you didn't see any down side--

DR. DONOHOE: That was just--in discussions with the FDA, there was interest in how much data we really had at that time point, and we started the SIRIUS trial not only addressing the acute thrombosis rates, or SAT rates, but also late thromboses, and we did have a good amount of clinical data from RAVEL indicating that they were not seeing a problem, but again, as a matter of just increasing the margin, we agreed with the FDA that we would add another month of antiplatelet therapy to a total of 3 in the SIRIUS trial.

But we had no preclinical data to say that that was necessary. In fact, in the clinical data generated, there is almost an equal amount outside the U.S. that again suggests that 2 months also provides equivalent protection from thrombosis as is seen with bare stents.

DR. WHITE: You are going to recommend 3 months in the U.S.; will that be the packet--

DR. DONOHOE: The packet right now purely summarizes the clinical data from the two studies, RAVEL and SIRIUS. I think one of the questions posed to the panel is what their feeling is about specifically recommending 2 or 3 months or a defined period.

DR. WHITE: Is there any reason to think that this stent will behave any differently for MRI safety?

DR. DONOHOE: No.

DR. WHITE: I mean, it should be the same as any metal stent; is that right?

DR. DONOHOE: Yes, that's right.

DR. WHITE: I would like to ask again about brachytherapy, because I think it's going to be a big deal. Do you have any reason from the company standpoint to be concerned about the application of brachytherapy in stent restenosis?

DR. DONOHOE: Well, within the SIRIUS trial, we have limited experience with brachytherapy of Sirolimus patients who have had restenosis. In fact, there were 7, and the average followup period has been 5 months, the longest has been 10, and none of the 7 patients have had any MACE events or adverse events over that followup period.

We also know that the dose given during brachytherapy is far lower than the dose required to chemically alter the polymer if you were to deliver a dose of radiation to the stent. So it appears from a theoretical standpoint that the dose from brachytherapy is not nearly high enough to actually alter the polymer itself.

So I don't specifically see from a company standpoint that we have any data that cautions the use of it. I would say that we don't have any data demonstrating the followup performance when there is failure following the Sirolimus-eluting stent, and we have very limited safety data at this point.

DR. WHITE: How long is the Sirolimus detectable in the vessel? What is the longest--I mean, is it all gone by 3 months? Is it all gone by 6 months? Is it there for 3 years?

DR. DONOHOE: For the slow-release, essentially 90, 95 percent of it is delivered over about a 6-week period of time.

DR. WHITE: So there may not be very much drug at all at 6 months?

DR. DONOHOE: No.

DR. WHITE: And the matrix that it is in, the polymer, is that also--

DR. DONOHOE: The polymer itself is a nonavertable polymer, so the polymer stays on the stent over the full length of time that the stent is in place.

DR. WHITE: The only last thing I would say--and Jeff, maybe you can talk about this--but is there any reason to think that physicians in clinical practice will be have any differently in their selection of lesions than your investigators did? I mean, you had 50 sites, so you had a pretty broad population of investigators.

We all know that we eyeball lesions differently than the QCA labs measure them, so I am concerned about the labeling issue--I want to label it the same way your investigators chose the lesions so that we get the same result. I don't want to label it according to the way the QCA lab measured the lesions.

DR. POTMA: I absolutely agree with you that you want to make certain that there is concordance.

I do think, to answer your first question about the lesion length, that between RAVEL and SIRIUS, we have indications for a full broad length of lesion lengths--

DR. WHITE: How far down did RAVEL go? They just had to be covered by 18, so--

DR. POTMA: By 18, so the average lesion length was 9, so the 50 percent--some of them were short. Now, I don't think that that necessarily in clinical practice means that you are going to treat a 5 mm lesion with a 8 mm stent, because I think your minimal effective dose was very, very effective, and I personally would be looking upon the 8 mm stent in the armamentarium to be the added conduit that I need when I am just a little bit too short with an 18, rather than add in another 18 mm stent, to have a shorter lesion for that period.

DR. WHITE: Would you be concerned that the 8 mm stent would do what you wanted it to do as a drug-eluting stent? Would you use a 12 or a 13 to make sure you got enough drug into--

DR. POTMA: For a short lesion, yes, I do think so, because we didn't go into much of the lessons learned from SIRIUS, but I do think, as Dr. Moses has indicated, that the restenosis when it did occur occurred at the edges, at an area where we don't think there was effective drug given to the vessel wall. And the one lesson that I think we might learn from the SIRIUS trial is we want to use a little bit longer stent-to-lesion-length ratio than we did in the SIRIUS trial, which was a 1.4 stent-to-lesion-length ratio, 1.6-stent-to-lesion-length ratio, compared to 2.2, which was the lesion length for RAVEL.

So the practical thing for the clinician is that they are going to use a longer stent for a 5 mm lesion. They are not going to use an 8 mm stent; they are going to go a little bit longer than that. And as Dr. Kuntz demonstrated in his presentation earlier today, we don't lose as much by putting longer stents in when it elutes Sirolimus into the vessel wall.

So the first question is, yes, we are going to be treating discrete lesions, but I do think there is a benefit--there was in RAVEL; and secondly, we are going to be stenting a little bit longer stent-to-lesion-length ratio than we would in our clinical practice. And I personally would look at the 8 mm as the added armamentarium that I need to use an 18, and not because I'm going to use the 8 to treat a 5 mm lesion, because I wouldn't do that.

Now, with respect to vessel size, we also went down to very low vessel sizes in SIRIUS--that was absolutely the case--and I think those were 2.5 mm stents in most cases. I think that we will learn more about our comfort with small vessel stenting. I do personally believe that a 2.25 mm stent is the appropriate stent for a 2.25 mm vessel--not a 2.5 mm stent--and I think much of the relationships that we saw with a higher restenosis rate, particularly at the [inaudible] restenosis rates in smaller vessels, relates to the fact that we didn't stent enough for the vessel itself, and I think a longer stent is going to be very useful in that circumstance.

DR. WHITE: But what do you think the QCA length is going to be for the 2.25 mm stents?

DR. POTMA: Do you mean to vessel diameter?

DR. WHITE: Yes.

DR. POTMA: It will be sub-2. But most clinicians--we get to follow every clinician in this country and how they do, and it turns out their balloon-to-artery ratios are pretty much 1.1-to-1.0, so what balloons they are selecting pretty much matches to what vessel size we are measuring. So they are not really doing such a bad job as the estimations go.

But there will be a little bit of a frame shift. We will call smaller vessels in our clinical trials than clinicians will use, but nevertheless I still think we have to have smaller stents to match this in the smaller vessel sizes themselves.

DR. WHITE: The question for us, though, is do we take modeling on sort of faith, without actually having experimental data to look at the results of that 2.25 stent. I mean, where do you come down on that?

DR. POTMA: Yes. I think the issue is not the stent size itself. It is very important--I think we all know the fundamental principle--we want to match the stent size to the vessel size. Do we believe that this is useful in smaller vessels? Absolutely. We believe that this therapy of a drug-eluting stent works in smaller vessels.

What we want to do as clinicians is to appropriately match the stent size that we take to the vessel size, so we don't get a margin dissection, so we don't get a perforation. So we don't want to leave us as clinicians to systematically oversize the stent to treat the smaller vessels.

I think we have plenty of data in our clinical trials to say that this works in small vessels. What we want to do is pick the right stent for the vessel size. That's the way I look at it.

DR. WHITE: That's it. Thank you very much.

DR. LASKEY: Jeff, just a variation--is there geographic miss in this study? Is that what I hear?

DR. POTMA: The question is was there geographic miss in this study. And then, I would have to say: Define geographic miss. It is very difficult. This is a very subtle concept.

We have looked very carefully at the pre- and post-dilatation balloons, and we have asked did we cause vessel injury at the margins themselves that were attributable to the pre- and post-dilatation balloon, and we have not been able to find a consistent relationship. That is some data that we will present at the HA.

However, the real question that we have is even though there is efficacy at the edges, we have to ask why is the restenosis rate a little bit higher at the edges, and I think there are a couple of different reasons for that, potentially.

One is that we are not truly stenting normal-to-normal. I have already mentioned the stent-to-lesion-length ratio that was different in RAVEL than it was in SIRIUS. I think that had we put longer stents in systematically, we would have gotten away from some of that edge phenomenon.

The second thing is that we also did not conceptually protect against balloon injury at the margins both with the deployment initially of the stent and also some issues about going to very, very high pressure--deploying at one pressure, pulling back a little bit, and then going to high pressure. And we didn't perhaps protect the margins as well as we should have.

I think the lesson for all of that is that we want to make certain that everywhere that we injure an atherosclerotic vessel--it may be different from a normal vessel--but everywhere that we injure and atherosclerotic vessel, we want to make sure that we have adequate coverage with the drug-eluting stent. I think that's the lesson that we have learned about geographic miss.

DR. LASKEY: Let me make a bold move here and try to get one more panelist in before the break.

Dr. Edmunds?

DR. EDMUNDS: I'm a surgeon, so you'll have to forgive me for a rather simple approach. But I look at this as a topical agent administered to the inside of a coronary vessel where the concentration per unit area is constant, and I really don't see all of these issues when the safety factor as I read the data is 17. The 17 comes from the concentration in nanograms per ml from the 5 mg dose that you use for kidney immunosuppression and the peak 1 nanomotor lasting less than an hour that you have observed with this stent at the fast-release--or, I guess that was the slow-release--reaction.

Is that a bad interpretation of what is

going on here?

DR. DONOHOE: I think that's exactly right, Dr. Edmunds. In this device, based on the questions asked about whether an 8 mm or an 18 mm stent still works, the main issue here is that we are keeping the dose per square centimeter--that is, the dose-to-tissue we are seeing per square centimeter--constant no matter what diameter or length stent is being used. And it is, as you indicated, compared to the systemic doses with Rapamune, significantly lower, and the tissue that is in direct contact with the drug or the drug-eluting stent is the tissue that is seeing the highest exposure to the drug.

DR. EDMUNDS: Two more quick questions--one is quick because they probably won't have the answer. Can you show me that restenosis curve beyond 270 days? Kaplan-Meyer curves don't have an end until the last of the oldest patient is accounted for. You have cut it off and would like to see the patients at risk. Do you have that data here?

DR. DONOHOE: We do not, no.

DR. EDMUNDS: Okay. That was quick.

[Laughter.]

DR. EDMUNDS: And you pushed out my last question.

DR. ZUCKERMAN: Maybe I could make a comment, then.

Dr. Foy, could you comment on why we don't have data past 9 months for the SIRIUS study?

DR. FOY: Per our regulations, when we send a filing letter to a sponsor, we are supposed to receive a 3-month clinical summary. We requested this information, and I believe David Kornhauser [phonetic] said that they had to cut their study of in August, so we would not be receiving a clinical summary with the 3-month update, which would indicate SIRIUS trial patients.

So we would actually like to see additional followup on those patients.

DR. EDMUNDS: I have had a quick recovery. The malapposition problem which you have seen in the Sirolimus group, do you see that as a likelihood to produce a dissection down the line of that coronary artery, and if a dissection would occur, do you think the stent could keep it from compromising the lumen, the true lumen?

DR. FITZGERALD: Peter Fitzgerald from Stanford again.

I think you bring up an interesting issue given that we have observed the stent struts that over time have detached themselves from the vessel walls. This is no a new occurrence with respect to drug-eluting platforms. It is an occurrence that we have seen with stenting in general. And we don't have that observation followed up long enough to be able to indicate what its rate of, say, generating aneurysms is, what its rate of thrombosis is.

One of the issues that I do feel comfortable with as an interventionalist is the ability for the stent to actually keep a dissection or some physical interruption in the vessel wall from migrating simply because the stent is encased in the vessel wall and providing some integrity and some strength to that vessel.

So if you have this incomplete apposition that was described in just bare metal recently in circulation at about 4 to 5 percent, it is on the proximal portion of that stent, so it doesn't really have the opportunity if it does create a dissection long term to go anywhere, because you have essentially a stent that is keeping that vessel somewhat more rigid, if you will.

So at least from a heuristic argument, I feel comfortable, although we don't have any support from data, but we certainly know in acute dissections when we stent them, we collapse the ability of that stent to migrate down the vessel.

DR. LASKEY: Peter, are you implying that you actually physically locate these malappositions more proximally in the stent than more distally?

DR. FITZGERALD: Right. In fact, the article that was presented just recently in Circulation, the vast majority are in the proximal area, and you have to wonder about why that may be. The vessels proximally are more tapered; they have an operated to not be quite opposed to the vessel well on baseline and then maybe have an opportunity long-term to have that small gap be observed, if we are looking for those.

DR. EDMUNDS: Well, sine we are all speculating, my concern would be that at the junction of the distal stent with the native vessel that you would create a dissection of the distal native vessel because of the stent presence. But it's all conjecture.

DR. FITZGERALD: Sure. But that may be different from this phenomenon that we are seeing over time of late incomplete apposition. I think you are absolutely right--any time you intubate metal into maybe unrecognized distal reference segment, whether it be a drug-eluting platform or whether it be a metal platform, it is that transition between metal and plaque that may certainly generate an edge tear. You bet. We have seen that clinically.

DR. LASKEY: Let's adjourn for 15 minutes, and let us please return at 4:15.

[Short break.]

DR. LASKEY: We have miles to go before we sleep. Thank you all very much. We are getting near that very special hour where everybody has to go somewhere, so let's adhere to the schedule.

If we can pick up with panel inquiries, Dr. Cantilena, please.

DR. CANTILENA: Thank you, Mr. Chairman.

I was wondering if I could actually ask a question to Dr. Throckmorton. Is that allowed?

DR. LASKEY: Anything is allowed at this hour. Go ahead.

[Laughter.]

DR. CANTILENA: Be careful what you say; you may get some unusual requests.

Anyway, actually, Dr. Throckmorton, if you could help with some of the numbers we were running regarding possible concentrations in blood in terms of the question of systemic exposure. If you look at the number for the highest dose--and I guess we have heard that that would be 1,500 micrograms, I believe--and if you look at that in the setting of expected plasma concentrations over perhaps 4 to 6 weeks, and let's put it in the setting of inhibition of CYP3A4 so that you get--and I guess the number for cuticonazole would be something like 10 or 11-fold increase in area under the curve--the question is does that get you into the situation where you would have overlap between systemic exposure from the stent and that which you would expect from low-dose exposure to Rapamune?

DR. THROCKMORTON: I am Throckmorton from CEDR.

I'm quite certain I would not be able to answer that question with any certainty. I imagine Wyeth-Ayerst could comment on that if they had that available. My sense is that you could probably find a situation where you might get close, at least in the initial placement. I don't know what the consequences of that would be; that is, I don't know what the dose response would be for some of the effects of Rapamune that people talked about this morning--the hypertrachlus [phonetic] edema and things like that. You made that point. It seemed an excellent one. It seemed like something that we need to talk with the sponsor a bit more about.

The doses do decline over time with this, and the sponsors presented some information about the in vivo release in humans, and again, that might or might not address your concern. The sponsor might be able to common on the upper dose limits and say the addition of cuticonazole or cuticonazole and a statin. But I know of no data exactly on that point from the available submission here.

DR. CANTILENA: Okay, but I guess the point is that if you were to extrapolate directly from the oral exposure using the concentrations that are given to us in the pharmacokinetic study by the sponsor, and then, I guess if you assume that it is a linear system and throw in the inhibition, isn't there a whole subset of CYP3A inhibitors that could get you into a situation where you would have overlap with systemic exposure that you would see from the low-dose Rapamune?

DR. ZIMMERMAN: Jim Zimmerman from Wyeth.

The answer to that is no. But let me recap this now. With a 1,500 microgram dose, we can project a peak of 6 nanograms per ml. But again, that peak is only one hour or two hours. And by 72 hours, that concentration decreases 40 percent.

You have to remember--I think we have to get a fix on this--the target levels for Rapamune are steadystate levels; they don't change, other than inter-subject and for subject variability. However, the stent is a moving target. It constantly changes. Although it looks like it is at a steady state down a terminal lesion, it is not; it is constantly decreasing. And as we heard, it would take approximately--well, it would take, I guess, about six or seven half-lives to get rid of the drug entirely. And if you make some estimates on that in terms of how much is measurable, for example, at 72 hours, you would be down to 3.6 nanograms per milliliter; another half-life, down to 1.8, down to .45. And if I count this, at about five half-lives, you can no longer measure the drug.

DR. CANTILENA: Now, if I could actually refer you to Dr. Hyde's summary on page 19 of his summary--and I guess it is Tab 4--he gives the confidence intervals--I believe they are confidence intervals; the percentile range with the lower limit for trough of 4.5 nanograms per ml on an oral dose of 2 mg per day. So my calculation was also 6 nanograms per ml, but I thought that this would fall between the ranges that Dr. Hyde has given. And again, these are averages, and I would just caution the committee that any drug that is cleared by CYP3A4 has across the population, the healthy population, a variability of between 5- and 10-fold in terms of area under the curve just because of the expression of that enzyme.

So if these are averages, then, can get to 6 just with inhibition, so if someone comes in for the procedure for the stent, and they happen to be on an inhibitor of CYP3A, I think you can probably see concentrations that at least overlap according to the calculations that Dr. Hyde has done. I was just asking for confirmation of that, but I can understand what you are saying, that the excursion into the overlap region would be transient is what you are saying, but the way my numbers and calculations work out, there does appear to be overlap.

DR. ZIMMERMAN: Well, this momentary overlap is not a problem. I think it is more important to see what is the clinical significance of that peak.

Could I see Transparency 17, and then we'll also look at 18.

[Slide.]

DR. ZIMMERMAN: This is 17. This was one of our first single-dose studies. We had doses up to approximately 68 mg if you look at a 2-meter individual, and the peaks are well over 100 into probably around 200 nanograms per ml. We did not observe any toxicity with peaks; in fact, we can give very large doses of Sirolimus without toxicity--single doses. That is essentially what a stent is, a single dose.

Can I see Number 18?

[Slide.]

DR. ZIMMERMAN: Here is another study. This is a multiple-dose study. And again, the peak concentration was up to 100 nanograms per ml.

I don't think it is important to compare where the troughs are, the steadystate troughs and that peak, because that peak is so momentary. It is really important how significant is that peak to toxicity, and it really is not significant.

DR. CANTILENA: I would just ask you--you are showing the results of steadystate, and this is sort of analogous, I think, but that's in a relatively clean population. If you look at the drug label for the Rapamune, you see a whole host of drug-drug interactions, which to my knowledge for a lot of these interactions, you don't really have a concentration effect relationship established. So to say they don't have clinical significance, I'm not sure that you can. I think that is an extrapolation. And that was my whole point of asking the question was that a lot of the adverse events, and a lot of the drug-drug interactions in essence don't have a concentration effect relationship for the Rapamune, and if you can achieve concentrations at least at the lower limit of what you observe at the low dose of the oral, then at least it is a possibility.

And I guess I would just ask you to be rather direct--are you excluding the possibility of a significant drug-drug interaction with the stent?

DR. ZIMMERMAN: This is my personal

opinion. I don't think there is a problem. Again, that's a momentary peak. You are down to 3.6--even at the highest dose, like a 1.5 mg dose, you are down to 3.6 at 72 hours. That short period of time is not a problem.

The other thing is when was the interacting drug given. Was it given simultaneously with the insert of the stent, or was it given 72 hours, 3 weeks later? I think it makes a difference in time, because as I said, the stent concentrations are moving targets; they are changing all the time.

DR. CANTILENA: Then, on the flip side, if you have someone who is on an inducer of CYP3A4 and has been on one chronically, what would the plasma concentrations from the stent look like, in your opinion?

DR. ZIMMERMAN: Again, I don't think it is a problem. I think inducers are even less of a problem because inducers have no effect of release of drug from the stent, nor does the released drug have any effect, I believe, on the concentrations in the artery.

DR. LASKEY: Thank you.

Dr. Ferguson?

DR. FERGUSON: Thank you.

First, let me say that I want to congratulate the presenters on what has been a magnificent, clear presentation, recognizing that you are talking to a surgeon here, even, okay?

I just have two questions. One gets to the point about the checkmate. When I read through the patient material at home, I was kind of struck by the fact that two pages-plus of the information for the patient had to do with the checkmate. And of course, now my concerns are even greater when I heard some of the comments that have been made today about that. I just wonder if you include this much material about checkmate, had you thought about the interaction situation prior to writing these?

DR. DONOHOE: The patient guide that we submitted, as you see, actually covers a variety of different approaches that could be offered. They weren't meant to be linked, and obviously, the patient is reviewing this for general information. Ultimately, the decision about what treatment option is taken is the physician's, and this wasn't provide for the patient to be making decisions on what treatment options are best for them.

DR. FERGUSON: Thank you.

The next an last question would be again the issue of the shelf-life. I didn't hear that, and I would like to hear a comment about the data which has been collected on the shelf-life for the stents vis-a-vis the drugs and the coating.

DR. DODINO: Good afternoon. My name is Ron Dodino, and I am vice president of Cordis.

In terms of the data that we presented, again, Dr. Foy has mentioned that we have actually responded to the questions that were asked. Stability was one of them.

We have offered data and have offered a proposed shelf-life to the Agency. What we would like to do is to discuss this with the Agency and propose a shelf-life together, moving forward.

So we have presented data on stability indicating method data for the products.

DR. FERGUSON: So it's not available for the panel?

[No response.]

DR. FERGUSON: I just asked a simple, straightforward question. If this is something that you want to work with the FDA on, that's fine, but I think the panel needs to know.

DR. DODINO: The proposed shelf-life is 12 months. Actually, that is the shelf-life that we have been granted for commercial product for sale outside the United States--12 months.

DR. FERGUSON: Thank you.

DR. LASKEY: I won't take much time. There are a number of more important questions.

Rick, this was a unique opportunity to look at drugs and their effect. Why was not dose put into your many models? You could adjust away for everything--how about a dose-effect relationship here?

DR. KUNTZ: That's an excellent question, Warren. I think one way to look at dose is our lesion length analysis, because there is approximately, I guess, 8 micrograms per ml. Therefore, the effect of length on restenosis could be associated with a measure of dose, but we'd have to disentangle the stent part from the lesion length contribution as well. So it would be hard to look at that.

Looking at dose-response relationship in general, probably the best measure of dose response would be the changes in dose per unit of tissue that the tissue sees, and that was intended to be fixed across all the different vessel sizes and lesion lengths. So therefore, we had one dose to analyze.

Other than looking at a whole artery dose per se, probably the best dose would be the dose that changes the concentration of tissue, and because there is only one dose available, we can't do a dose finding relationship in that respect.

DR. LASKEY: It just seemed like a unique opportunity to look at something very fundamental, and with all due admiration, you are the master of teasing things apart, so I was looking for it in all your models, but I missed it. But clearly, absolutely dose irrespective of per-square-centimeter would have been an interesting way to look at either dose effect or dose toxicity.

DR. KUNTZ: Yes, I think you're right. I think that outside of the notion that we're probably looking at fixed concentration per unit of tissue, the absolute dose would be interesting to look at, and we would probably have to integrate the length and the size and get that information, and it would be a good thing to do.

We did it by looking at stent length, but

I think you also get more dose on bigger stents as well. So we would have to do some kind of cross-reference of those two.

DR. LASKEY: Dr. Aziz?

DR. AZIZ: I too enjoyed the presentation, and I am a surgeon, so I think some of my questions may be directed that way.

Let me ask if any patients in this study ended up going to surgery, emergently or needing surgery?

DR. DONOHOE: I don't believe any in the active treatment group went to a surgeon on an emergent basis.

DR. AZIZ: If there is a patient--I'm sure it will happen--who does need to go to surgery, do you have any suggestions--I'm sure somebody must have thought about it--for what would be done about the corporate vessel? I mean, can the stent be removed? Can you cut across that, or would you have to go beyond it?

DR. DONOHOE: I think--are you talking about bypassing into that vessel--

DR. AZIZ: Yes.

DR. DONOHOE: --the stent would be treated as you would a bare metal stent at this point, so if your option were to go into that stent and cut through it, you could potentially do that if you wanted to go distal. But the issue that would be relevant in terms of the difference between a bare stent and this Sirolimus-eluting stent is the fact that we have a polymer and a drug on board.

Over the period of time that we have talked about in the 6-week period in which essentially 90 or 95 percent of the drug is released, beyond that point, there is essentially no drug effect in that tissue. So in terms of the tissue healing response, it should not be any different than the bare stent.

In the shorter term, if bypass is done in that [inaudible] area, as we discuss, the rate of endotheliazation seems to be the same with or without Sirolimus present, so I would think that in terms of the endotheliazation that would occur an estomatic site would be uninterrupted also.

DR. AZIZ: And just going back to the other problem that has been addressed earlier, the incomplete apposition problem, if you looked at the patients who did have that, let's say, diabetics who were the patients who had more calcification in the vessel, was there any particular common denominator or thread or similarity in those patients?

DR. DONOHOE: No. It is a relatively small sample size to be looking for those factors, but we have looked at them, and we haven't seen anything in common. The only observation that we thought was a bit out of line with the general proportion of diabetics in the study is if you look at all the RAVEL patients, the 10 that had incomplete apposition, and the 7 SIRIUS that had late incomplete apposition, there was, I think, only one diabetic in that whole group. That was the only item that we found that [inaudible] the proportion of patients.

DR. AZIZ: I think somebody else asked this question earlier, but I'm going to ask it again. You mentioned that one patient had an autopsy, and you were able to look at the actual stent in place. Is that the only one patient in all the studies that was actually looked at at autopsy?

DR. DONOHOE: Only one, yes.

DR. AZIZ: Okay. Thanks.

DR. LASKEY: Dr. Pina?

DR. PINA: First of all, I want to thank

you for your patience with all of our questions here.

I am bothered by a bigger issue here. We are dealing with a drug that, as far as I know, has never been approved for atherosclerosis, placque reduction, injury, except for T-cells and perhaps even B-cells in transparent patients, and maybe, Dr. Throckmorton can explain to me if this gets approved, what happens to the labeling of the drug, because everything that is in here pertains to the renal transplant for which the drug is approved. We use it for heart transplants all the time, and true, there is some data in there about maybe less vascular injury in our transplant patients, but that has not been clearly documented, and I think vascular injury in transplant is very similar to post-angioplasty injury. It has endothelialization, it has media increase--very, very similar.

So here, we are dealing with actually putting a drug onto the vessel, and yet I hear very little about the chemistry of these patients, I hear very little about the side effects of the drug, and yet we are giving a drug for a purpose that we have never given before. And this is not a totally benign drug. It needs to be used appropriately. Now, I agree--it is small doses, it is probably not doing anything, but I think you at least need clinical lab data, and I just haven't seen any.

I don't know what to give these patients. I don't know whether to give them statins. I would hope they would be on statins. I would hope--again, I made this point earlier--I would hope that they would be on ACE inhibitors for vascular remodeling.

So we are giving a drug directly onto the vessel wall, and this is the first time that I have ever seen this in a device. We are not just treating the lesion by opening it; we are treating the lesion by chemically giving a drug that I haven't seen any data yet in animal studies, for example, that this is really a drug that works. I know it is anti-inflammatory, but how much of the inflammation is involved in the vessel and in the changes that happen after angioplasty?

So I am asking to go back, and I would even like to know why Sirolimus. There are other anti-inflammatory agents. What was it about this drug that was so specific and so unique that Cordis chose to go to this drug with Wyeth--and it is a fine drug on transplant; we use it all the time; we use it in difficult patients; it is a terrific drug to use in transplants.

So one of my questions again is regulatory. Here, we are approving a stent with a drug for a purpose that the drug as far as I know has not been approved for, and maybe Doug can help me clarify this.

I have other questions, but I'll start off with this one.

DR. THROCKMORTON: One question I think I can answer, and one question I am quite certain that the Agency has not yet come to a place where we can answer.

[Laughter.]

DR. THROCKMORTON: We are talking here just about the drug-device combination, so this will have no impact on the label for the approved drug product as it is administered as a drug for systemic use. That was the easy part.

The hard part, and the thing that we have not yet finished grappling with, is the description of the drug component of the drug-device combination here. I share your concern about the need for adequate information to patients about the drug aspect of this combination in the same way that I know Dr. Zuckerman worries about the adequate description of the device part of this combination for patients. Both of those parts have to be adequately placed into labeling.

For the drug, we are going to have to make decisions about what aspects about the consequences of known systemic administration as far as adverse events, drug-drug interactions, monitoring, a black box warning--how many of those pieces would need to be in this label for safe and effective use. And without speaking for Dr. Zuckerman, I think we are a fair way away from finalizing that discussion.

DR. PINA: The sponsor said that they actually had data available for lipid levels and statins and background medications on the patients. I'm sure you must have collected that on your CRF forms, and I'm sure you have CRF forms. This was a randomized, blinded trial. But we haven't seen any of that, so I am having a hard time even characterizing the patient population other than that they have a lesion, and I don't do angioplasty--I am a noninvasive cardiologist, but I take care of patients with coronary disease--I would like to know what this population looks like, if this is a population that I am going to send to my colleagues, and they may indeed have a stent placed.

Do you have that data, or will you be supplying that data to the FDA?

DR. POTMA: Jeff Potma. I actually had the unique opportunity of personally reviewing about 80 percent of these angiograms, and I can tell you that the patients have focal disease where they had their stent as influenced by the clinical trial design, but they had the disease of atherosclerosis in their other vessels.

I would echo your comments about the importance of lipid-lowering therapy and secondary prevention measures, but not to treat the 15 to 25 mm segment of vessel where we are trying to prevent the intimal hyperplasia. The points that you are making about secondary prevention are points that need to be done in all patients who present to us with atherosclerotic disease. They all need to have their LDL cholesterols of 70 or 80. That is part of the normal clinical practice.

The one piece of data that I would refer you to in the panel pack itself is the frequency of recurrent out-of-hospital myocardial infarction, which Dr. Donohoe mentioned earlier. Actually, if the hypothesis is that the patients who receive the Sirolimus-coated stents do worse because of pertubation to those levels, you would not expect to see a statistically significant lowering of the non-Q MI rate as you did in this trial.

So I would argue that this is doing very important effects--one, to emphasize what you are mentioning, that you have to lower lipids, and you have to take care of secondary prevention--not for the 20 mm of segment that we stent, but for the other 200 mm of vessel that we leave behind with atherosclerosis. Specifically focusing on the area where the stent was placed, there were actually less out-of-hospital non-Q-wave MIs in those treatment groups because the disease of restenosis was prevented.

So I don't think that there is evidence in the clinical data with respect to out-of-hospital recurrent MIs, but there is a higher incidence. In fact, you could argue that the incidence is lower because you prevented restenosis.

So to echo your comments, yes, all patients, interventional cardiologists, noninterventional cardiologists, should know that lipids need to be lowered, ACE inhibitors need to be given, beta-blockers need to be given for all patients with atherosclerotic disease. And the patients in this trial were very similar to the patients that I treat in my clinical practice. But if we focus on that area that got the drug-eluting stent, the actual recurrent MI rate was lower, not higher, in those patients who received the drug-eluting stent for the out-of-hospital no-Q waves.

DR. PINA: Thank you, and don't move for a minute, because this is probably also pertinent.

There were also early myocardial infarctions--there is a little bump in that curve early on the drug-eluting stent. They are small numbers, but can you talk about those?

DR. POTMA: Actually, if it is okay with you, I would like to defer to Dr. Kuntz, because those would be in the confines of peri-procedural MIs. Some of the issues about the CKMD versus the [inaudible] criteria may come up.

I think my comments were specifically out-of-hospital MIs, so maybe I could refer to Dr. Kuntz about the pari-procedural MIs.

DR. PINA: You may want to tell me something about why triponines weren't measured, since the middle triponine leaks.

DR. KUNTZ: We didn't measure triponines in this study systematically, because not everybody had triponines available to measure. This study was initiated 3 years ago, and there was a lot of [inaudible] deciding whether we would measure triponines. But not everybody had triponine available, and there wasn't a standard established at all the hospitals for the normalities like there is for CKMD.

I think that if you are focusing on what is the impact of this drug-eluting stent, the concomitant medical therapy in the atherosclerosis portion of the patient disease, per se, just following up on Jeff's comments, we viewed the segment that is obstructive and easily treated as transforming into a scar needs to be prevented.

With respect to disease that can occur at the nontreated segment, which was about 95 percent of the coronary we don't put a stent into, we do have two measures of atherosclerosis progression. One is the instance of MIs that Dr. Potma talked about, which was similar between the two groups, and the other is the incidence of nontarget lesion revascularizations which suggests new lesions that pop up and then you revascularize, which is usually around 2 to 3 percent, and they were also evenly distributed. Actually, the estimate was a little bit lower in the Sirolimus arm than it was for the control arm, but we would assume they were the same.

So we had no evidence that the use of this stent caused any increases in classical atherosclerosis manifested events over the course of 9 months in followup as new lesions that grew or MIs that occurred.

Now, with respect to the peri-procedural MIs, it is a very interesting issue, because in our field, we are focused on measuring even small levels of cardiac enzyme elevations because of the legacy from the IIbIIIa inhibitor trials, as the IIbIIIa inhibitor trials have demonstrated definitively that they can reduce MIs, and the best signal of measurement is when we actually measure slow levels of MI using the CKMD rated at three times normal.

This is traditionally a definition that you would use if you are trying to use a device or a drug to prevent peri-procedural complications. Classically, in the stent studies, we generally are interested in restenosis, so we have always used a less sensitive and more robust definition of MI, which has historically been the World Health Organization definition of MI, and that is a CK greater than two times normal, which happens to be very much less sensitive than CKMD at three times normal.

So if you are doing a study of IIbIIIa inhibitor's impact on acute complications or embolic protection devices, you would want to use the one that is very sensitive, because that is how we can distinguish what is good. But if we are looking at a stent study where we are trying to evaluate impact of restenosis, you don't want to drown out the events of sensitive peri-procedural MIs, we want to make a more robust definition, and hence, our interest in using the WHO definition.

We have the data broken down both ways. When we looked at the peri-procedural MI part, it was equally distributed between the two arms. There was no evidence to suggest, either using the robust definition or the sensitive one, that there is an increase in peri-procedural myocardial risk associated with the implantation of a stent.

And the conventional wisdom about what causes those heart attacks is twofold. One is that there might be some distal emboli particulate that goes downstream, and the other is there might be pinching of some old side branches that may cause the small embolization. And they seem to be equally distributed between the two arms.

DR. PINA: All right. Let me follow up on your point about the clinical events, either Q or non-Q or acute coronary syndrome.

What about angina? Do you have any functional data, noninvasive data of ischemia, on these patients? I'm sure a lot of the physicians actually got noninvasive studies, sine that's pretty common.

DR. KUNTZ: Right. This is also an excellent question. It is something that we have been wrestling with for a long time in clinical trials in the studies that we have performed and I know that others have performed. We have not been able to completely classify angina in these kinds of studies unless we use instruments like the [inaudible] questionnaire or other quality of life instruments.

So in studies where we are looking for devices or drugs that generate new vessels, like angiogenesis devices, angina becomes a very important issue, and it is a very comprehensive, frequent application of instruments by experts, like the quality of life questionnaire, the [inaudible] questionnaires, that give us some measure of angina.

We didn't use that in this study because the typical failure mode clinically, whether right or wrong, has been the requirement of repeat revascularization determined by the physician and the patient in making the decision to come back into the hospital and getting repeat revascularization.

The reason that we use that more robust endpoint is because there are 85 different ways of doing noninvasive testing, so it is very hard to standardize that unless you actually put into place a core laboratory and require people to do that. Having participated in studies where we tried to establish Bruce protocol or modified Bruce protocol for the exercise test, we still have huge problems in what people call "modified Bruce," for example, so it is impossible for us to enforce a functional study at 4 to 6 months to go forward, and that has been very difficult to do in stent studies in general.

Moreover, the reproduction of their initial symptomatology, which is probably the best measure of angina--jaw pain, chest pain, or shortness of breath--has also been quite difficult to do in these studies because many times, patients enter into a study without classifiable symptoms per se. They sometimes come in because they have heart failure, and they get diagnosed with a tight stenosis, or they have other measures of functional ischemia but no symptoms per se.

And because of that heterogeneity, we have never really relied on measuring angina in having outcomes in stent studies, so we have always traditionally focused on two endpoints--again, right or wrong, we don't know--which is measurement of a narrowing portion with a sizable subset that has angiographic followup, and the clinical need for repeat revascularization that is externally adjudicated by a committee that would say that given the unique data of this patient on a patient-by-patient basis--that is, return of their chest pain and a positive stress test, however it was done, and the findings of the cath lab, validated by a core lab--the committee would agree that that was an appropriate revascularization, and that gets counted as an endpoint.

That is why we have ended up with these extremely robust endpoints of repeat revascularization rather than common frequency of angina.

Now, after all that explanation, we do have measures of angina that we can actually calculate, but I just think they will be noisy in general; but we can summarize those.

DR. PINA: I agree with you that there are lots of different ways to look at ischemia--some people like ECOs, some people like stress. Do you have any functional data, regardless of how the investigators did it? Every center may have their own way of doing it. I know we like dilbutamine [phonetic] ECOs.

DR. KUNTZ: We do capture in the pre-revascularization categorization, CRF, we do actually document what functional study they had and what symptoms have they had. That is actually almost a narrative form, because the potential set of all possibilities is enormous, and it would just be a matter of classifying those, and trying to do that before, you have lots of bins with lots of different counts and so on, but this is a large enough study that we could actually try to do some collapsing of endpoints to get a measure of angina.

DR. PINA: I think it would be an interesting piece of information to see how much ischemia--you've got a lot of diabetics, so you're going to have a lot of people who have no pain but in fact may have a positive study, a positive noninvasive study.

DR. KUNTZ: Right.

DR. PINA: I have no more questions, Mr. Chairman.

DR. LASKEY: Dr. Bailey?

DR. BAILEY: I want to also compliment the sponsor as well as the FDA. This is one of the more informative packets that I have seen. I will focus primarily on statistical issues.

I think the data on face value form a pretty good overall picture of benefit with respect to the endpoint that was the primary endpoint. This primary endpoint is obviously not an angiographic endpoint, and it is really not exactly a clinical endpoint in the sense that out in the real world, people don't get angiograms 8 months after they have a procedure. So the blip that we have seen really is, you might say, an artifact, or at least at a very minimum, if you really wanted to estimate the impact of the therapy in the absence of routine angiography, you would probably want to extrapolate those lines out to wherever and hope that your extrapolation was correct.

So I think we can appreciate the endpoint, and it is very dramatic, but keep in mind that it is not really a pure clinical endpoint--"pure" isn't the right word to apply to a clinical endpoint, I guess--but it is reasonably convincing.

I wanted to ask one question on this issue of blinding, which I think you can belabor, but revascularization is an elective procedure. You were just talking about stress-testing. If you were to try to categorize the reason for revascularization, it would be interesting to see what percent of the time it was for symptoms or for ischemic response versus just 50 percent stenosis. And indeed it would be interesting to look at the rate of revascularization conditional on the percent stenosis compared between the two treatment groups.

I don't really think that blinding is a serious issue here, but it is sort of a nagging concern whenever you have a somewhat behavioral endpoint. I wonder also if one wanted to create an endpoint that was perhaps less susceptible to the behavioral issue, what about taking all of the early revascularization as nonelective in the sense that the angiogram was early because it was motivated by something, but then, instead of taking revascularization at the routine angiogram, look at the percent stenosis and put that together. So in other words, it would be sort of a composite endpoint where you would take the early revascularization as a real clinical endpoint, but when you get to the sort of study angiogram, then just look at the percent stenosis and see whether there is a 50 percent restenosis or not.

So that is my thinking on the endpoint, and I don't think it is a major concern, but I think it would be helpful to know how often the reason for revascularization was just the fact that you see the 50 percent stenosis versus something prompted doing something to help the patient for some other reason.

Now, having said that, as I said when I

started, I think the overall results are fairly compelling, and I think the main issue is what patient population it can be extended to. And I think most of the comments that have been made around the table here, I would agree with, in particular the fact that you have got to apply the indication to the method that the people use out in the world to select the patients. So it has to be made very clear that if there really is a systematic bias with quantitative coronary angiography, one should make the indication correspond to the visual readings, or else one should reanalyze the data perhaps that way and see if that makes any difference.

This is sort of a dilemma. In any clinical trial, you have an overall result, and then, how do you apply the results to--what patient population do the results apply to?

It is fortunate when they are as strong as they are here, because you feel more comfortable applying them at least to the patients within this study. But I really do have serious concerns about extrapolating the results beyond the borders of the patients who were recruited into this study, and that is where I think the different models that Dr.

Hyde presented or that Dr. Kuntz presented--we can disagree about what the most accurate model is, but the point is they are all plausible, and it is very important which model you use when you go to trying to extrapolate them beyond the boundaries of the patients recruited into the study.

I would argue that even within the boundaries of the patients in the study, if you have a very small fraction of patients in a certain category, it is hard to know exactly how strong the evidence has to be with that specific subset.

Clearly--and again, it is the same dilemma we always have--say your results apply to men and women, but you only had five women in the study. Obviously, that's not fair. Well, what is the right number? That's a hard question to answer. But I think we are most comfortable when you can use internal data without making any assumptions, and of course, usually, we don't have the power to have that luxury.

So I think I would tend to come down that I am fairly comfortable applying it to the patients who were recruited into the study, but I am not very comfortable extrapolating beyond that because of a sensitivity to which is the right extrapolation model.

And by the way, I think that, yes, it is true that--I would refine the comment that Dr. Kuntz made that biology is linear by saying that most biological studies that we do don't have the power to detect nonlinearity.

I think we are all in agreement that the exclusion of the patient who didn't meet the entry criteria even though they were already randomized is legitimate. I would just prefer to say that it is legitimate even though it is not an intent-to-treat analysis. Let's humor the statisticians, and let us keep the purity of that term, but go ahead and defend your right to do something else. I think that is reasonable.

Okay. I guess I should make at least one comment about the historical controls. I think this is a reasonable thing to look at in terms of comparing the previous experience with the angioplasty patients. However, I guess one question I have regarding that is it is not the Bayesian analysis, it is a Bayesian analysis. I think it is commendable to incorporate the variability amongst those results in the different studies, but why are we then referring to the mean of those results rather than the best of the results for angioplasty? It is not really the most conservative analysis you could do, although I think I heard someone say that the results, if you just took the best angioplasty results, were still significant.

But relevant to this same issue, I think I heard Dr. Hyde or someone else comment that the definition for the main endpoint was different, or the current definition of MACE was different than it had been in the previous angioplasty studies. If that is true, I think that that is a very important thing that would need to be addressed before relying on this comparison.

Getting back to the endpoint, I wonder if, had the results been looked at by subsetting which group had angiography--in other words, are the results similar in the group that had angiography versus the ones that did not--that would be one way of looking at this sort of observation bias.

I think those are my comments.

DR. KUNTZ: I'll address those issues which are very valid, and thank you for those comments.

With respect to understanding how to

determine whether someone appropriately got treated or not when they came for angiographic followup, the Clinical Investigation Adjudication Committee, because it is blinded, has an algorithm that they follow. In general, they require--and this is a committee of approximately 10 cardiologists who meet every Wednesday night to discuss these issues and have done over 8,000 cases in followup in the last 5 or 6 years, and it's the same crew--they require anybody who has a narrowing between 50 and 70 percent to demonstrate some level of either recurrent angina or functional study in a case-by-case unique basis. So when a patient comes back and gets treated, we should have the angiographic data.

For narrowings less than 50 percent, and someone actually treated them, they require extreme data like a very early positive functional study, or else they would discount them. Then, they can't look at it as clinically-driven.

If it is between 50 and 70 percent, they require at least recurrent angina on a narrative or a cap report [phonetic] demonstrating a functional study or the functional study itself.

And we have extensive researchers who go out and find this stuff if it is not in [inaudible] form. And in general, if the stenosis by QCA is over 70 percent, most people would agree it is probably appropriate that the patient came back, because it is hard to explain how a 70 percent lesion or tighter, especially using the current QC algorithms we have, would not be human anatomically important. So they do use that.

And when they do find those approaches, on page 57 of the panel pack, in Section 531, you will see that there are those patients with clinically-driven and non-clinically-driven [inaudible] adjudication to demonstrate which ones actually get thrown out and which ones [inaudible].

I'll just read the numbers for you. The clinically-driven TLRs is 4.2 percent for the Sirolimus arm versus 16.9 percent in the control arm. And those cases actually received TLR, but the committee actually threw them out. It was 1.9 percent for the Sirolimus arm and 4.0 percent for the control arm. So actually, there was almost 2-1/2 times more rejection of TLRs in the control arm that were inappropriate [inaudible] Sirolimus arm.

So that just shows the mechanism of how

the committee works and what they actually do to determine which ones--

DR. BAILEY: And they were rejected because--what--less than 50 percent stenosis?

DR. KUNTZ: They would have less than 50 percent stenosis without controlling systems, 50 to 70 without recent function study [inaudible] would be the main reason to throw them out. So they review each case on their own, and since they are blinded, they determine whether they were actually clinically-driven, taking all of the [inaudible]. So the data is internally consistent with them acting in a way to screen, to try to get appropriate--

DR. BAILEY: But the don't screen the non-revascularizations to see if that is appropriate.

DR. KUNTZ: They also do screen the non-revascularizations.

DR. BAILEY: Do they?

DR. KUNTZ: Yes. So that we have another form for followup, that if patients have a positive angina or function study in their clinical followup, they actually investigate those individuals,and if they have a positive stress test and have not had an angiogram, or had an angiogram but were not treated, that's another signal that comes up.

DR. BAILEY: So is your endpoint based on the appropriate treatment?

DR. KUNTZ: Correct.

DR. BAILEY: So it is sort of an intention to treat.

DR. KUNTZ: You will find in an American interventional investigative group that not too many people squeak by without being treated. So that possibility--

DR. BAILEY: How many changes were made?

DR. KUNTZ: I am not quite sure. There may have been just a half a percent or a percent that actually get upgraded, but we actually have those numbers, and we can give you those. But we do upgrade some who don't get treated, but it is not often that we see that with investigators, especially if they come back with angina or a study.

So to your point that the angiogram does interfere with the clinical outcome, there is no question it does, and that's why we put all these mechanisms in place that try to minimize that effect.

I think the point that we were trying to make was that the frequency of those patients who have those lesions that had to be adjudicated was four or five times higher in the control arm than it was in the active arm, and that's why you will see more events occurring there. Even if it were evenly distributed with no bias, you would expect to see more events occurring just because the opportunity is there; there were more narrowings in that group.

The other important point is that one could ask why didn't we just view this study on a clinical basis--and we would have all loved to have done this clinically as well, but we--and I think the FDA would agree--also know that it is important to get angiography followup on these patients as well. It is important to look at the angiogram, because we have discovered in some forms of radiation therapy, for example, and others, that there are patterns of restenosis that actually suggest harm or problems associated with that, and in looking at a new therapy, the angiogram actually is a very important way to measure the mechanism of narrowing. And there are certain patterns that we are familiar with that are good and bad patterns.

So necessarily this was actually a pretty rich and large angiographic subset because we wanted to have power to detect any kind of endpoint that might be problematic, including the observation of late aneurysms, which we can detect by angiography, and patterns of [inaudible] stenosis and others that we have seen with other therapies, for example, de novo radiation therapy.

So we were caught between a rock and hard place in trying to provide a study that was large, comprehensive and had elements of angiographic followup that would apply to those data and clinical followup. We tried to strike a balance by having about two-thirds of the patients required for angiography and one-third not and look at those cases overall with these mechanisms to try to minimize any of the interference that might happen from the requirement of a late angiogram.

The second question you talked about was extrapolation, and again, as Dr. Hyde pointed out, this is the art of statistics and how to actually look at the data per se.

I think there are a variety of different ways to evaluate the models, and I think that they are all kind of exciting, and from linear and nonlinear models, we learn a lot about how patients respond.

I think that you are right that in the boundaries of what we have brought in as eligible--and I think if we were to focus on the dimension of lesion length, 50 to 30, we have pretty good evidence that it worked in those ranges. That is, when we took patient who were 20 mm or greater--although, as Dr. Hyde pointed out, it only represented about 20 percent of the cases--there was still significant benefit even in that subset on [inaudible] analysis for Sirolimus compared to control. And our estimations might be different--there might be a reason to use nonlinear versus linear, and we have certain preferences and so on--but I think that in general, the data itself looked like it was relatively constant when we broke them into their bins over that range.

So the fact that the boundaries of the patients--we asked patients to come in who had 50 to 30 mm in relation to length by the investigators; we used a randomized trial that was positive in substantial portion, and when we looked at the S demands [phonetic] over that bridge, they still seemed to preserve the same distance of benefit overall, and the subsequent analysis of those greater than 20 still showed statistical significance.

I feel pretty confident that this thing works within 15 to 30 mm per se. Can we extrapolate beyond 30 mm? Well, we start to get to a point where we have less than 10 percent of beta above 30 mm, so it is going to be difficult to extrapolate at that level.

If we look at the dimension of vessel size per se, we actually started with 2.5 to 3.5, but we did still work with smaller vessels and slightly higher vessels per se. If we look at those zones of extrapolation outside the boundaries, they do continue in their S demands, but they do fall off in their power to detect that.

If you were to invoke that at 3.5 to 4.0 mm, the vessels would change in their physiology so that they wouldn't show the benefit--or, for example, 2.25 or down--then, you might be concerned that we don't have enough data to make that inference per se. But I think if we go from the values of 2.5 to 3.5 and look at the leaks that go over, I feel confident that we can show a benefit from 2.25, at least, and probably a little bit over 3.5, because the data are very strong. And as you know, when the vessel gets smaller, they have [inaudible] that is where we stand [inaudible] of those boundaries, but I think I agree with you that within the boundaries of the eligibility, I think it is pretty solid; extrapolating much beyond that is very tricky.

DR. BAILEY: Not the eligibility, but what you actually get.

DR. KUNTZ: Well, there is one thing [inaudible] your next point, which is if you tell an investigator to do 15 to 30, and then you actually get 10 to 40, we have to understand what it means to get a label for 15 to 30, because if they continue to get 10 to 40, obviously, you may end up with what you tell somebody [inaudible] what you actually get.

So the most conservative approach, I think, would be to look at the boundaries of what the criteria were to get into the trial, because that is what we ask the investigators to do, and then we got back this sample which is slightly wider than that.

So I think the decision to go either to

the boundary itself or the eligibility or slightly beyond that just depends on how confident you are about the population group or the sample size and the zones.

DR. LASKEY: Can I ask a question here? This is the best look at the data. When you apply these models to the population that was developed, it gets worse from there. So this is your best shot, and if it's tenuous at the end, it's going to be even more tenuous or maybe not even P equals NS when you get to not this population.

So do you want to qualify these models as they apply to the fringes?

DR. KUNTZ: Actually, I think this gets into some hairy statistical stuff, and I think the issue is that you lose power once you go to the edges of anything. If you look at any sample space for which we define the eligibility criteria, and the core of that was in the central part of the sample space, and we go to the edges, most of the time in randomized trials when you have a positive result, you actually make an inference about what the eligibility criteria were. That is classical in a randomized trial.

In this situation where we observe areas, we have two ways of telling whether the treatment effect is effective. One is to look at the overall power for the individual small zones on the edges, and we lose power because the sample size falls off.

The other is to look at the actual raw estimates themselves, and the raw estimates do maintain their distance out at the edges.

So I would say that the data is consistent with working at the edges, it is just not proved that that small area is independent to show that.

DR. BAILEY: I think Dr. Hyde presented the various cutoffs and found that when you lumped everybody over--what was it--3.5, I think, it was significant, which would tend to imply that at least the applicability goes somewhere into that range, but we don't know how far.

DR. KUNTZ: Just to finish up the last few points that you made, the small vessel analysis, which was an analysis in which we pooled three previous trials using Bayesian techniques to add a component of variance for between-trial variance, projected an overall S demand of the outcome which was a central estimate and not a high estimate. That's how we ended up with the noninformative prior.

This is a technique that we have used in estimating large sample size of the stents and trying to look at registries and seeing it there if a new registry matches up with an adjusted prior distribution from, say, a bunch of stent trials. That technique is helpful because in this special case, we will never see a study in the future of balloon angioplasty versus stenting for small vessels. Stents are so prevalent right now that we can never envision that we would ever be able to perform a [inaudible] study using balloon angioplasty in one group versus stents in another in America. I just don't think that is going to happen.

However, there were four studies done in Europe and in Canada, and four randomized studies with sample sizes between 300 and 500 patients demonstrated in two studies no difference between balloon angioplasty and stenting and two studies demonstrating a significant benefit for stenting.

So four studies with over 1,200 or 1,300 patients demonstrated that the stent in small vessels is at least as good as balloon angioplasty and possibly better.

So with the combination of a Bayesian analysis and the fact that the patients with small vessels had benefit for Sirolimus compared to control, I think it would be safe to say that the Sirolimus is at least as good as or significantly better than angioplasty, because the stent arm in four randomized trials has demonstrated that stents are the same or better than balloon angioplasty. Hence, the system of Bayesian analysis where we actually used previous studies in the balloon angioplasty era to pull back in.

So neither of those approaches is obviously direct randomized data, but I don't think it is possible to do a randomized trial anymore of standard stenting versus balloon angioplasty.

But those pieces of information are actually pretty strong, I think, as indirect support to suggest that this has benefit.

DR. BAILEY: Obviously, there is always the issue of historical controls. I guess my point was that you used the mean of the three, but the most conservative approach would be to take the best shot, the best result, for angioplasty. That was all.

DR. KUNTZ: Right. I understand.

You had a final comment about angiography per se--I can't remember what the comment was, but maybe I addressed it in the previous comment.

DR. BAILEY: Analyzing the data by the subgroup defined by who received routine angiography.

DR. KUNTZ: Yes. That is performed, and we do have that analysis as well. We do have an analysis that separates out those patients who were prespecified to have compulsory angiography versus those with just clinical followup per se, and we see the same differences. We just see a lower rate, as expected, in patients with clinical followup without introduction of angiography. So as in every study we have ever seen--

DR. BAILEY: You have similar separation, but not the blip.

DR. KUNTZ: Right--similar separation in a distance, but the blip is in part due to actual deserved clinical difference in restenosis, and obviously, some component is driven by the angiogram that we will never be able to get out even with [inaudible].

But the data is consistent in those cases that didn't require angiography, and we still have the same difference in clinical outcomes when angiography wasn't interfering with their evaluation of clinical [inaudible].

DR. LASKEY: Before we get to the panel discussion of the questions to us, does anybody have a single, solitary question to ask of the group or the FDA?

Yes?

DR. KRUCOFF: Actually, I lied to you, Warren. I have two singles.

I have one question for FDA, and I guess I'm sitting here, just trying to sort out this whole small vessel business. As I look at it, and I look at the distribution here, what the original trial design that was approved as an IDE did, if I understand you all correctly, was approve the use of an unapproved bare metal stent in patients down to 2.5 mm vessels, randomized against an investigational combination of a stent with a drug-eluting polymer-coated surface in patients with 2.5 mm vessels.

Is that right?

DR. ZUCKERMAN: Yes. The original intent of the trial was to try to design a real-world trial, and that's why the inclusion criteria were

2.5 to 3.5, less than 30 mm.

A frequent criticism of FDA previously has been that in the coronary stenting trials, we have evolved into a situation where our approved stents are in a range that only covers about half of the patients treated in the United States, which is not ideal. We can debate ad infinitum why that has happened, but here was a chance to try to get data in a more realistic range--the 2.5 to 3.5 range.

The tradeoff that FDA accepted was that in the 2.5 to 3.0, the control and the randomized trial would be a bare stent. That is why kind of as additional external data, we looked at the Bayesian methodology in which we were able to impute what would happen if we were actually able to include a balloon angioplasty three-arm trial.

There was never any intent from FDA's perspective for this type of trial then to result in a request from the sponsor to result in a labeling basically where the whole world of coronary artery disease could be stented in one sense. Again, where one has a label from 2.25 to 5.0, given that lesions are in the eye of the beholder, this kind of implies that significant lesions are amenable to treatment with a drug-coated stent.

We would see the need for doing a--usually, our advice is to do a trial in this median range, the 2.5 to 3.5, the small vessel range and the larger vessel range, which might include SVG graphs.

DR. KRUCOFF: So, of the it looks like 268 if I'm reading this right--patients with 2.0 to 2.5 vessels who were randomized primarily in this trial, did the informed consent document actually tell patients that if you have a small vessel, you are going to be randomized between two investigational therapies?

[No response.]

DR. KRUCOFF: Okay. Then, my last question--I happen to agree with Rick. I don't think there is a chance in the world that you could do a trial against plain balloon angioplasty in small vessels because it is simply not being done in the community. And you can acknowledge that, but I think that with acknowledging that, we ought to just analyze the data from a randomized trial where you have 124 patients in each.

Now I go back to your tables, Rick, which were not in the panel pack, so I'm going to apologize for missing this on the first pass. But what I don't see out of all your 16-cell tables is the primary endpoint. Am I missing that? Do you have these tables for target vessel failure?

DR. KUNTZ: We do have the analysis, and we didn't bring that, because we were trying to use it to look at restenosis per se, because the risk of restenosis is worth focusing on.

I don't think we have that data--

DR. KRUCOFF: All right. Just because I think ultimately, at least for me, the issues are going to be not what the inclusion criteria are for approval and for labeling of the product, but outside of the inclusion criteria, where do you go on assumption or on data, it would be helpful for me to see that.

And just as a double footnote, your manuscript--it is a four-by-four table, not three-by-three.

But if you have these tables for target vessel failure, that would help me.

DR. KUNTZ: Yes. My guess is that if we did it for target vessel failure, the treatment effects would be lower because target vessel failure adds to MI and death, so it would round out, and my guess is that the averages would be in the 40 to 50 percent range for treatment effect overall for the TVF part, so therefore, 60 to 80 percent for the clinical restenosis. That's the main difference in TVF and TVR.

DR. KRUCOFF: In the big vessel/short lesions and the small vessel/long lesions?

DR. KUNTZ: Well, we know that the main driver of TVF is the TVR component. It is about 90 to 95 percent of the components of TVF. So we would be looking at almost a map of the same thing. We would just be adding equally to both arms one or two percent of death and MI for the cells, and they would be extrapolated because there weren't that many deaths and MIs that have been followed. So it would be just like adding one or two percent per cell. And when you bring both up, the differences become relatively lower.

DR. KRUCOFF: That's assuming that in fact it is not related to size or--

DR. KUNTZ: Well, I can tell you what that is right now, because we don't see that these things ever have influenced MI. We have actually looked at those, MI and death, which is a very low frequency, and we have never been able to find a significant predictor. So we would have to extrapolate out the average.

Questions and Answers for Panel

DR. LASKEY: At this point, I think the panel is hopefully prepared to address the questions put to us, so Drs. Donohoe and Kuntz, thank you, squared. You have been very helpful. Thank you so much. I'll ask you to step back.

If we could put the questions up now and move on.

Is anybody on the verge of leaving for the airport? Dr. Bailey, are you okay? Okay, everybody is staying.

This is the part of the meeting I enjoy the most--developing consensus.

The first question? I am pro-MAC. This is addressed to Dr. Waxman and people at TCT who are MAC-hostile.

DR. ZUCKERMAN: Dr. Laskey, since you have the questions, do you just want to read them?

DR. LASKEY: That's fine with me.

Okay, Panel. The first question is on evaluation of safety.

"The safety endpoints evaluated in the SIRIUS study included: MACE to 270 days; with the

7.1 percent versus 18.9 percent rate at 270 days; stent thrombosis to 30 days, 0.2 percent in Cypher, 0.2 percent in the bare stent; and late thrombosis to 270 days, 0.2 percent in Cypher versus 0.6 percent."

"Do the data submitted on the Cypher product provide adequate assurance of safety?"

[Pause.]

DR. LASKEY: I sense there is consensus amongst the panel that it does provide assurance of safety.

DR. WHITE: Can you better define that? Is that safety to 9 months? Is that long-term safety?

DR. LASKEY: As they apply to the data provided to us, to 270 days; we have not seen safety data beyond 270 days, so I think our comments for acceptance of this data are limited to that. We would like to see additional data, and I think that will be forthcoming in additional comments.

The second question, along the lines of evaluation of safety: "The applicant has requested approval for a range of stent diameters and lengths and corresponds to a nominal drug dosage as high as

399 micrograms. The animal studies conducted by the applicant on doses higher than 180 micrograms were limited to 30-day study. The SIRIUS study only evaluated 15 subjects who received stents with a total nominal drug dosage greater than 350 micrograms."

"Given the limited preclinical and clinical information outlined, please comment on whether there is adequate evidence to support the use of stent diameters and lengths--that is, 4.5 mm and 5.0 mm diameter with a 33 mm length--with a nominal drug dosage greater than 350 micrograms."

DR. KRUCOFF: Can I propose that we actually address drug and polymer in this and the very next set of questions together, since I think the issues are largely around dimension and whether or not there is data to support it?

DR. EDMUNDS: Let's answer the question; it just confuses me.

DR. LASKEY: So we do not have adequate evidence in this range?

DR. EDMUNDS: I disagree. We have shown no evidence that there is really any systemic toxicity to this drug. It is a topical agent, and it is proportional to the amount of release to the amount of area that it touches. I don't think we need to complicate it any more than that.

DR. LASKEY: Do my colleagues concur?

DR. KRUCOFF: I don't think we have any data in these areas, and I think the answer to the question has to be that there is no demonstration.

DR. WHITE: I would concur with that, Mr. Chairman, on systemic exposure--I have already spoken to that.

DR. LASKEY: Along the lines of what--and I think this is a good time to interject the carrier issue or--however you want to call it--the polymer issue, but when the drug is gone, all that is left is the polymer. We don't have any idea, other than extrapolating the experience with this polymer in joints and lenses, what the action of that, quote, "inert" polymer is on the vessel wall.

We do know that there are many carriers of other substances which elute other substances which are highly toxic to the arterial wall by themselves. So I agree with you that we can't divorce the carrier from the drug, particularly when the drug is gone. So that remains an issue in my mind, and I think we should develop some verbal consensus on that issue.

DR. WHITE: But Warren, I guess I'm asking--I would defer to our pharmacology colleagues here--but what I heard presented--and I guess we don't have evidence of this--is that there are different doses with the stent, but it is evenly applied along the stent, and the way these devices will be used will induce, I think, a large variability in the total dose received.

It would be nice to see what the gentleman, I think, from Wyeth said, which is that it doesn't matter--I mean, that it is such a short peak that it doesn't matter. It would be nice to see some dose-response data that assured us that even at toxic levels, it wasn't.

Maybe that just hasn't been presented plainly or clearly enough to us, because he seemed to be pretty comfortable that from the oral doses of this drug, it didn't seem to matter very much.

DR. CANTILENA: I would just comment that in terms of systemic exposure, this is sort of an ongoing slow release for up to 6 weeks. In the calculations that I did with Dr. Throckmorton, we started with the slide that was shown by the sponsor as a total dose of 150 micrograms, resulting in a peak concentration of 0.6, and then we heard that the highest dose would be exactly 10 times that, which, assuming linear, which I think you can, you are up to 6.0, and then, in the worst-case scenario, if you have an ongoing inhibition of CYP3A, you would increase that also by a factor of 10.

So I think there is the possibility, which I think can be easily confirmed with a short study that can easily look at that.

DR. LASKEY: That would be the answer to (b). I think it is fair to say that the panel does not certainly have consensus on whether there is adequate data here. Given that, there might be adequate data with, as you suggest, Dr. Cantilena, an additional study of drug dosage, systemic dose at doses greater than 350 micrograms.

Good.

DR. KRUCOFF: I just want to reemphasize the difference between--we are talking about a topical application versus a systemic application, in an environment where I think we all would have a lot of questions about how important it is to cover--to use a little longer stent as part of the topical application. That is where I just don't see that we could say that we have data, other than by doing what to me would be a pretty straightforward extended registry or subsequent study to get the data.

DR. LASKEY: Are you happy with that, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. LASKEY: Okay.

"Additionally, the nominal amount of total polymer ranges from 208 to 1,184 micrograms for the currently requested range of stent sizes. The animal studies conducted by the applicant on polymer dosages higher than 500 micrograms were limited to 28-day followup. The nominal total polymer amounts tested in the SIRIUS study ranged from 208 micrograms to 520 micrograms."

"Please comment on whether there is adequate evidence to support the use of stent diameters and lengths--that is, 6-cell and 7-cell stents in lengths of 23, 28, and 33 mm and 9-cell stents in lengths of 18, 23, 28 and 33 mm--with a nominal polymer dosage greater than 520 micrograms."

I think the answer is "Not really; we don't know."

"If not, what additional studies or

information would be necessary to support the safety of stents with a nominal polymer dosage greater than 520 micrograms?"

Well, the same answer, but I would probably ask for an additional length-of-time study. Again, if we are looking at the effect of polymer when the drug is gone, I would probably look at more than 28 days.

DR. EDMUNDS: Warren, I object. We don't have the data--that's a given--but I don't think the question is relevant when we haven't shown that there is any systemic toxicity at the doses that we're talking about.

DR. LASKEY: I'm not sure if this is about systemic toxicity, Hank. This is toxicity to the wall, perhaps.

DR. KRUCOFF: Or the different between an intentional--

DR. EDMUNDS: You have no data to show that there is any injury to the wall.

DR. KRUCOFF: But there is no data to say that if you line 60 mm of the wall with this stuff--which the "full metal jackets" concept here is very much in the therapeutic potential of what would be the best result or what might open a whole new door of unanticipated results.

DR. EDMUNDS: If you've got a rash one inch square, and then you have a rash three inches square, you just add to the surface, and the dose and the surface go up together linearly. That's the way I see it.

DR. CANTILENA: If I could just respond to that, you do have evidence of systemic exposure--blood levels from the stent--so you can extrapolate that if you increase the dose, you will probably increase the concentrations in whole blood. So that's your systemic exposure, and then the drug label talks about the relationship between systemic exposure and adverse events.

So I think it's not that much of a jump, and I'm just saying that you don't have the actual studies here, and there is a reasonable chance that the toxicity is probably going to be significantly lower from the stent. But if you get back to plasma levels or--excuse me--whole blood levels, you do have the possibility of comparable exposure at the higher dose. It is not something, I think, that is extremely far-fetched.

DR. EDMUNDS: Can I respond?

DR. LASKEY: Please.

DR. EDMUNDS: In a transplant patient, you get 17 times the highest dosage, and you do it chronically, and there is no problem attributed to this drug.

DR. AZIZ: I think in the transplant situation, you do get higher lipids as a result of that. Although these levels aren't as high as the transplant group, I think we should bear that into account, that there is an effect of higher levels in transplant patients.

DR. LASKEY: And we're not talking about transplant patients here.

Yes, Chris?

DR. WHITE: And the other thing is to keep in mind the difference between the systemic drug issue and the local polymer issue, because the polymer issue is not systemic; the polymer issue is the artery. The sponsor described an inflammatory response. What happens in 2 years?

DR. LASKEY: That was my point, exactly.

We don't have consensus, but we all agree that we need more data.

The third question along the evaluation of safety: "In SIRIUS, the Cypher group had 19 percent rate of incomplete apposition at followup versus 9 percent for the control." Obviously, this is incomplete apposition by IVUS. "This included a 10 percent rate of late incomplete apposition for Cypher versus zero percent for the control. In RAVEL, the rate of late incomplete apposition was 21 percent versus 4 percent for the control."

"There was no obvious clinical correlation between late apposition and adverse events. Please comment on whether additional information is necessary to evaluate the significance of late stent malapposition found in the clinical studies."

I think it is fair to summarize that the panel is saying we don't know what it means, whether it is just an IVUS curiosity or has potential clinical significance, and that followup beyond the data provided to us is certainly something that we would be interested in seeing, if not requiring.

If I'm not mistaken, does RAVEL not go out to 2 years? Don't we have 2-year followup on late stent malapposition in RAVEL--18 months. So you have some of this, but again, it's an issue that needs to be put to rest in terms of whether it is a curiosity or a marker for adverse events.

DR. ZUCKERMAN: I guess the question that

I have, Dr. Laskey, is that during panel discussion, note was made about the small numbers in the IVUS cohort, and what we could conclude. While perhaps part (a) of your answer to please comment on whether additional information is necessary is to continue to follow those who have gone down the IVUS track, is there a need for larger numbers to be studied with IVUS to fully answer this question?

DR. LASKEY: Well, here, we can play the statistical came, and maybe Kent Bailey can help us out. But we have a rate in this study called the "biased subsample" of IVUS, but there is information from the recent Gary Mintz [phonetic] paper on a baseline rate in a relatively unselected, non-study population for what this is. So there is information that to my mind would justify continuing to follow these people and not recruiting another whole cohort--but I am willing to listen to my colleagues here for consensus or lack thereof.

DR. KRUCOFF: I think that mandating additional IVUS procedures relative to the cohort reported in patients who are already enrolled would seem counterproductive to me. My understanding--I guess we'll get to it later--is that there is a plan for 5-year followup clinically in these patients, and out of a 1,000-patient cohort, if there were a significant problem, I would hope that that would surface as a clinical problem, that close attention to angiographic variables gathered in later clinical problems would make sense.

The one thing that I might encourage would be if additional studies are done per the previous questions just answered, with longer stents or higher doses with greater drug and greater polymer exposure, I would certainly encourage both the sponsor and FDA to think about incorporating IVUS observations along the way, again, just to see if, relative to currently-tracked rates, it looks any different or behaves any differently.

DR. LASKEY: Bearing in mind that it is not angiographically detectable, and the definition may vary from site to site as well. This is a technically dependent kind of finding, but you all need to standardize that.

"Is there any specific targeted followup--additional testing, animal studies, bench-testing--that could be requested to contribute important information regarding this clinical finding?"

I don't know if this is a clinical finding yet; it is a finding, an IVUS finding, perhaps of incidental significance, perhaps not, but I wouldn't call it a clinical finding yet, and I would just agree with Mitch that we need more information, certainly long-term followup.

What do you think, Kent?

DR. BAILEY: I think at a minimum just followup of the patients who already are known to have had late malapposition, or any malapposition, and if they are okay after a few more years, that's good news.

DR. LASKEY: "In the RAVEL study, subjects received aspirin for 6 months and clopidogrel or ticlopodine for 2 months. In SIRIUS, subjects received aspirin for 9 months and clopidogrel or ticlopodine for 3 months. Please discuss your recommendations for antiplatelet therapy for patients receiving the Cypher product."

I think the general rules have always been do what the study protocol mandated, and I don't think we would recommend anything different than that.

Chris?

DR. WHITE: I'll just stir that pot and say that it's a financial burden on the patients and that there is no evidence of any late healing problems or late thrombosis; there is no reason to be suspicious. And I would expect Marty Leone [phonetic] to quickly publish a paper that says that only 30 days is necessary for this, so it will change our clinical practice very quickly.

But I would be happy to accept the RAVEL protocol as supporting information so that we can recommend maybe less than 3 months' burden for our patients and still feel comfortable that we have met the safety.

DR. PINA: Chris, what do you do now?

DR. WHITE: I actually try very carefully to titrate or to select patients with more of a vascular burden to treat with chronic ticlopidine or Plavix, and I try to take patients who have less of a vascular burden and be sensitive to the cost of treating them. So I don't treat everybody the same.

There is a minimum of one month of Plavix that I think we all agree, basically, that we use, but the people that I put on chronic therapy have more vascular disease than patients who have simple limited cardiac disease. I don't think everybody needs Plavix for life who has coronary disease.

DR. PINA: I just think that we have a larger trial that has 3 months and 9 months of aspirin, and most of these cases are going to be left on aspirin anyway, because they will have vascular disease.

DR. WHITE: No--I agree with the aspirin part. But the question is do we want to set the standard in the labeling that really requires every physician to not deviate from that standard if we don't feel that it is really necessary.

I think that's what it comes down to is RAVEL was only 2 months; it looks like there is no problem with late thrombosis. Why are we automatically picking 3 months without some reason?

DR. ZUCKERMAN: I think there is a regulatory issue here to consider. Both clopidogrel and ticlid [phonetic] are not technically indicated in the PDR for this indication, so our general standard has been in stent labeling just to describe the way the unapproved drugs would use.

We would certainly encourage the sponsor to do the sorts of more efficient studies that you recommended so that we could describe in the labeling just other conditions. But there is a certain line that we don't want to go further than in this application here.

DR. LASKEY: Although lessons learned from brachytherapy would tell us otherwise

DR. ZUCKERMAN: That's why we would encourage the sponsor to get the data. There is a precedent here with the STARS [phonetic] trial and the former development of stainless steel coronary stents.

DR. LASKEY: Committee members

DR. KRUCOFF: Morty, I think that gives you 32 days.

DR. LASKEY: What are we recommending

DR. KRUCOFF: I would be with Ileana just to start with the level of recommendation that is appropriate for a drug that is not approved, but to start with the protocol--that's the data you've got--but recommended, not necessarily required--the SIRIUS protocol.

DR. LASKEY: I can't help but think about what Jeff Moses said when he finished here. He said we have altered the molecular milieu of the artery. We have done that, and I think we need to be safe.

Question 5. "The potential for interaction with several drugs has been evaluated as described in the Rapamune labeling. Interactions with other drugs might be expected based on known metabolism by CYP3A4."

"Please comment on whether the application adequately addresses drug interactions that are likely to be important or of interest."

I think we can do that right now. No, it is really not.

"If not, what other information or studies should be requested?"

Mitch?

DR. KRUCOFF: Just one question I didn't think to ask before, but is there any known cross-reactivity, allergically? Are there any other drugs that allergic reactions imply might cross over as an allergic reactivity to Sirolimus?

MR. __________ [Unidentified speaker]: The class if drug is a macrocyclic lactone, which is actually different than some early confusion with macrolyte [phonetic] antibiotics, so there is actually no cross-reactivity with erythromycin or the other mycins, and it is a relatively distinct class.

The only other related compound is tacrolimus [phonetic], which also doesn't show significant hypersensitivity reactions.

DR. LASKEY: Lou, do you want to restate it

DR. CANTILENA: Yes. I think that in terms of studies that should be done, it would be a very straightforward pharmacokinetic, drug-drug interaction study with inhibitors of cytochrome P4503A4, and all depending on the magnitude of the effects observed, and that would sort of impact on the labeling, which we will talk about later.

DR. LASKEY: And those could be done in a handful of patients; is that right--typical pharmacokinetic-

DR. CANTILENA: Yes. It should be done probably, depending on the expected effect size, usually for CYP3A4 for polen [phonetic] inhibitors. In the oral situation, which this is not, you can usually easily get away with 6 to 12 subjects. But certainly it is unknown exactly what the effect size would be here because of the route of administration.

DR. LASKEY: Again, I just want to

reiterate something that I said earlier, which is the interaction with the HMG cholate reductase [phonetic] inhibitors, which may be started along with the stent implantation in patients who weren't on it preceding. So that's a very common drug, and we ought to look at that interaction for systemic toxicity.

"Has the followup been adequate to address concerns about possible systemic adverse drug effects?"

I think it has.

Question 6. "The primary effectiveness endpoint for the SIRIUS study was target vessel failure rate at 9 months, 270 days. Rates of TVF at 270 days were 8.6 percent for Cypher and 21.0 percent for the Bx Velocity control group."

"Does the evidence presented on the Cypher product provide reasonable assurance of effectiveness at 270 days?"

Actually, it is efficacy, isn't it? And I think it does. Can we all agree? Yes. Thank you. We'll see about the effectiveness soon.

Question 7. "Prolonged inflammation and notably increased restenosis were observed when polymer-coated, but drug-free, stents were implanted in swine. In swine implanted with Cypher product--that is, coated with both drug and polymer--this effect was not observed at one month post-implant, but was observed at both 3 and 6 months post-implant."

"Given the unparallel timeliness of healing between juvenile and normal pigs and atherosclerotic older adults, do these findings raise significant concerns about the ability of the clinical followup to address the possibility of a similar delayed occurrence of neointimal hyperplasia?"

I think I have heard that they do.

Dr. White?

DR. WHITE: I guess I'm not sure that they do. The question is at what point--how late. We have already said that 9 months is probably not enough to be completely sure. But I'm not highly suspicious that there is a downturn in any of those curves. So I am pretty comfortable, but I would like to see that later data, I guess.

DR. LASKEY: Okay. I think we all agree with Hank Edmunds' comment about seeing more of the lines going beyond 270 days for event rates.

"If so, please comment on whether

additional testing or followup--pre- or post-approval-- is necessary to support the effectiveness of the Cypher product."

Again, I think that by observing the SIRIUS population out beyond 270 days, we may have the answer. We probably will.

Question 8. "The temporal relationship between scheduled angiography and revascularization, and analysis of the subgroup that did not have angiography, suggests that angiographic outcomes may have influenced the clinical outcomes in a way that differentially affected the control group."

"Please comment on the adequacy of the primary 9-month TVF endpoint for capturing the expected clinical benefit of the Cypher product in light of the possible influence of 8-month angiography results."

I think we have discussed this extensively here in the last hour, back and forth, and I think we are all satisfied with the explanation, and we understand the limitations of this approach, and we have known time and time again that rates in populations that don't undergo routine angiography are always less than those that do.

"Are there other ways the clinical impact should be assessed, either for a) evaluation of efficacy in determining the appropriate indication, or b) for information to be conveyed in labeling?"

Well, I think if we're sort of comfortable with the paragraph here, I'm not sure we need to look for ultimate ways de novo.

Mitch?

DR. KRUCOFF: I do think that an analysis in the same structures as presented but using sight or visual reference vessel diameter and lesion length would be informative just to make sure it is not inconsistent with what the QCA results showed.

DR. ZUCKERMAN: Well, Dr. Laskey, can we go back a moment on this question and go back to some of the points that Dr. Bailey raised as to how the angiography causes a blip in the Kaplan-Meyer curves which are perhaps artificial.

Certainly these trials evolved from our initial stent experience in our intracoronary brachytherapy experience where it has been very important to look for edge effects and to use the angiogram as a mechanistic instrument. And certainly we know from some European drug-coated stent trials that the importance of angiography for picking up safety effects has been demonstrated again.

On the other hand, to have three-quarters of the total patient population getting followup angiography perhaps is overkill, overpowered, and biases the interpretation of the true clinical effect.

So I would like Dr. Bailey or Dr. Laskey to comment on how much angiography is necessary, but is there a better way a) to temper it and b) to perhaps indicate if it is worthwhile to perhaps indicate in a label the clinical restenosis rate in patients who do not undergo followup angiography--i.e., is that a true representation of effectiveness in the real world

DR. BAILEY: I think I agree with everything you said. I think we were reasonably convinced that given you are willing to accept appropriate revascularization, which I would say because all these people got angiography is not entirely a clinical definition, nevertheless I think the relative efficacy was shown, but certainly the clinical impact would be better estimated by the people who didn't get routine angiography.

But one suspects that--I mean, a good fraction of the revascularization events occurred prior to that time, so it is just sort of a little--

DR. WHITE: These patients were still blinded, so the decision to overutilize and overtreat should have been distributed equally so it doesn't affect the efficacy of the device--I mean, the device is still powerfully effective; we just may have overutilized.

DR. BAILEY: The question, though, is how many of those who were revascularized would have eventually come to attention and gotten it anyway.

DR. WHITE: Is that important?

DR. BAILEY: Well, some of those people may never have had any problems.

DR. WHITE: That may be true, but I don't think that that impacts on the trough.

DR. LASKEY: We're kind of torn here, and I thought that Rick Kuntz expressed it quite well, as usual. You need to decide whether you want to look at the biology here or the clinical efficacy, and your biology--you needed to learn what is going on here, so you needed angiography, you needed pictures. If you just wanted to do a TOR study,it would have been your preference to do a TOR study. That's the clinical restenosis rate in the real world.

I think that what we are grappling with here and the reason we are in this soup is because the study was designed to really look at both of these issues, and you have the biology and the angiography, and then you have the clinical relevance, but even that was strongly statistically significant albeit in the 15 or 20 percent of the group that didn't undergo routine angiography, so the effect is preserved in that small group, too, but it is a very telling lesson.

You look puzzled.

DR. EDMUNDS: But the donut is still the high line in the stent group of low restenosis. The hole is the loop in the control group.

DR. LASKEY: And?

DR. EDMUNDS: Well, the point is that the stent works. It gives you a much lower restenosis rate than we have seen clinically, and it was demonstrated angiographically in this study, and that's the point

DR. KRUCOFF: I agree. I think no matter how you slice it, including at the 7-1/2 month point, the biology and the clinical are very consistent. I don't think it's "soup"; I think it's pretty consistent

DR. ZUCKERMAN: The point, though, is I don't think anyone disagrees that within the context of this trial, the drug-coated stent is effective. It is more in the labeling. What is a better guesstimate of what the true clinical rate is, and it is perhaps in those--the question is, is it in those patients who don't get followup angiography, and should that be indicated.

DR. LASKEY: I think you can report both outcomes in the labeling and just leave it at that. If you wanted to do a TOR study, you should have done a TOR study. Certainly reporting both is nothing to be ashamed of. Both are very positive.

DR. WHITE: Bram, are you concerned that you are going to magnify the--I don't understand the concern, because stress and Benestent [phonetic], all of those trials are angiographically driven endpoints. When we quote restenosis rates to patients, we are quoting these angiographic rates. So that quoting the stenosis rate isn't the same as the number of people who are treated. It is still not going to change the people who had more than 50 percent restenosis rate.

DR. ZUCKERMAN: The reason why I ask this question is that we are just concerned with truth-in-labeling and the labeling of the coronary stent. Table 17 that Drs. Bailey and Kuntz discussed is a very telling table because the evidence of the occulostenotic reflex, which was between 20 and 30 percent in both groups, i.e., revascularization with questionable clinical symptoms based on angiography, is a theme that we have seen for the last almost 10 years in stent versus stent trials, and reflects a certain rate that you will see in a clinical trial where angiography is necessary. But for the working clinician who wants to appreciate what the effectiveness of the device is, it is perhaps not the only number that one should consider.

That's all.

DR. LASKEY: Therefore, report both

DR. PINA: Mr. Chairman, I think that, Bram, may be where the noninvasive testing would come in handy for information, because that's what is most commonly done. We don't ordinarily cath at 6 months or at 8 months or at 9 months. I don't know--Chris, do you? What do you do?

DR. WHITE: No, we don't. But I think the interventional cardiology community is fairly comfortable with this data, and we understand the dichotomy of what is being discussed here. This is part of our daily life.

The occulostenotic reflex is there. You get angiogram and--look out--you're going to get something done to you.

The problem is that the noninvasive tests are not accurate enough. I mean, we all have stories of--we don't want to divert to anecdote here--I think reporting both is fine. Knowing what the restenosis rate is I think gives adequate information. Not everyone with restenosis needs to be revascularized for a clinical endpoint, and that is I think what Bram's point is. We ought to just report that.

DR. LASKEY: "Because the control stent is not approved for de novo stenosis in vessels of diameter less than 3 mm, the applicant provided additional analyses, including a Bayesian comparison to historical angioplasty data. Please comment on whether adequate evidence has been presented to demonstrate the effectiveness for stents with diameters less than 3.0 mm."

We are intrigued by the Bayesian analysis--Kent

DR. BAILEY: I like the point that I think Dr. Kuntz made that looking at the historical data makes us comfortable using the bare stent as a control.

So I think if we could resolve what subset of patients in the SIRIUS study benefitted and whether it can be extrapolated beyond that--I think Bayes is nice, but it is the GI/GO thing. You can't really get more than you put in.

So I think that is useful, but I think I like the idea of going back to the bare stent as a reference group.

DR. LASKEY: I don't think the reservation we have is with 3.0 or perhaps even 2.5, but when you get down to 2.25, that's where we are not particularly happy no matter how much hand-waving that is.

I think that summarizes our level of acceptance. Yes.

"Univariate regression analyses of data collected in the SIRIUS study suggests that the treatment effect may be reduced in longer-length lesions. This could be due to either a true diminished treatment effect or a lack of power--too few subjects--to detect a treatment difference in subjects with longer lesions."

"The applicant has performed logistic regression analyses, but these analyses only included main effects and did not specifically evaluate the possible interaction between each variable and the treatment effect."

I thought you did; I thought you showed early on-

DR. ZUCKERMAN: The question was written before the sponsor presented a very late analysis that has not been fully evaluated by FDA.

DR. LASKEY: All right. But this business of post hoc power, that because you don't find something, you just don't have enough power, I thought that was a statistical no-no. You have power going into a study, but you have one power, and that's it. That's the power of the study, to find the difference. You can't really then backtrack after it's done and say, "Here is our power; we were underpowered"--isn't that correct?

DR. WHITE: I think he's talking about subsets

DR. BAILEY: Right.

DR. WHITE: It's underpowered for the subset of this whole thing.

DR. LASKEY: Okay.

DR. BAILEY: Right. The study wasn't powered to detect--and most studies aren't powered to look at interactions, although this one comes pretty close because of the fact that the treatment effect is very large does suggest that there might be power to look at subsets.

But the other point is what is the right null hypothesis--and I think Dr. Hyde brought this up. Usually, we say with the null hypothesis--we are trained to say the null hypothesis is no interaction, so we've got to see data to prove that there is an interaction. But here, the conservative approach is to assume that there is a subset treatment interaction. So it should be a whole different way of looking at interactions, not demanding high levels of evidence that there is one, but showing that the data aren't consistent with enough of an interaction to make a difference.

DR. LASKEY: So therefore, "Do the data presented provide reasonable assurance of effectiveness for treatment of the full requested range of lesion lengths, including less than 30 mm?"

DR. KRUCOFF: I just want to mention again that there was an inclusion lower limits as well in this study that is not reflected in the request for approval, which is where we are talking about by going lower than 30, also going lower than 15. And I am as concerned about where data doesn't exist in shorter lesions, which we all know have lower restenosis rates when stented, and what has been provided as data supporting effectiveness.

DR. LASKEY: I guess you're dealing us a hedge here. "Reasonable assurance of effectiveness"--look at the curves, I think there is reasonable assurance--it's not solid; it's not as though you did a head-to-head randomized trial in those regions of vessel lengths, but it is reasonable.

Do we agree?

DR. WHITE: I kind of like what Mitch said, and that is that I think we--in clinical practice, we are not going to limit a practitioner's ability to treat a lesion that needs to be treated on an individual basis, but I think if we say that the data for the investigators were 15 to 30, and we found effectiveness for that data, then I think that that is where that stands. I see no desire to push that any lower than--there is no reason to go any lower. And it doesn't limit how we treat patients, and it is a conservative approach for us to take

DR. ZUCKERMAN: Okay, but the dataset under consideration by this panel today is the RAVEL data, the SIRIUS study, and the First-in-Man, with the RAVEL data being lesion lengths less than--what is it; 15 or something like that--

DR. WHITE: And to be covered by an 18 mm stent; right?

DR. ZUCKERMAN: Correct.

DR. LASKEY: Those lengths on the order of 8 or 9 mm; right?

DR. EDMUNDS: Can I just say something? In practice, if somebody has a 7 mm lesion, is he going to put in a bare wire stent, or is he going to put in a 15 mm coated stent? That's reality out there.

DR. WHITE: But in reality, what we decide today doesn't really impact that very much in that I would like to be able to stand behind what we say today in the future, and I feel very comfortable about 15 to 30.

It may be okay to treat 12's or 8's, but I feel very comfortable about 15 to 30

DR. KRUCOFF: Yes, I think we have to remember the distribution curve. Even in the 15 to 30, in fact, the bulk of the distribution is in one section; it is not evenly distributed across 15 to 30. So at 15 and at 30, we are already tailing off, and I think that that is expectable, I think that is normal in a prospective design, but--

DR. WHITE: It goes back to Mitch asking for the site-specific data, and that is that my eyes see 15 mm, but Jeff Potma measures 11.2. I mean, I think we want to target our recommendations to what the investigators were trying to do.

And I guess I have trouble with RAVEL because I didn't get a good feeling for the comparability of the short studies in RAVEL, whereas this trial seemed to be better.

In fact, there is a graph that I looked at on page 112 that actually looks at terciles of lesions treated and compares them for the coated and uncoated stent, which is data that I was interested in, and it actually demonstrate across each tercile, small, medium, and large, the efficacy of the stent. That's the kind of data that I think makes sense. It doesn't deal with lesion lengths. Was there a lesion length table like that? What page? Help me, because that's really good for the diameter, because it tells you exactly what they got.

DR. DONOHOE: [Inaudible comment; no microphone.]

DR. LASKEY: Does that cover lengths and diameters satisfactorily? Okay.

"Does the data presented provide reasonable assurance of effectiveness for vessel diameters of 2.25 mm?" This should be an easy one. No.

Thank you.

"One aspect of the premarketing evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse events. Please address the following questions regarding the product labeling."

"1. Comment on whether the Indications for Use statement identifies the appropriate patient populations for treatment with this product."

"Has the application provided reasonable assurance of safety and efficacy for treating the full requested range of vessel diameters--2.5 mm through 5.0 mm."

I think we just answered that for you, that at the extremes, it does not. And, panel members, where do we want to pare things down--to the study inclusion--

DR. WHITE: Could I just draw the distinction in my mind as an interventionalist between the diameter range the length range is that the length range is at an individual operator's discretion, and that I can treat as long or as short a lesion as I like. But if we limit the diameter, that means that I will not have the ability to treat a 2.25-size vessel because it won't be made, it won't be sold.

So the length business becomes--we can be very conservative--but I think the diameter, we ought to be more liberal.

Does that make sense? No, it doesn't

DR. KRUCOFF: Hell, no.

[Laughter.]

DR. KRUCOFF: I think it's called "data," Doctor. I think the inclusion criteria are the center, the focus, of a trial that was prospectively statistically designed to answer and has clearly shown efficacy and safety in the boundaries of that trial, even though we know there are, again, tails out to the sides; those tails in diameter to are just as fuzzy, Chris, as--

DR. WHITE: But on page 112, if you look at the small size, the mean diameter that was treated in the small tercile was 2.32 mm. Now, that's QCA, and I think that's the rub here, but the range of those diameters was 1.48 to 2.56. So I think that you get pretty far down, and I don't think it would be a grave injustice not to accept this QCA data on the low end of the curve. I think it's all judgment, because there is some data to support 2.25. It is not just drawn out of thin air, and it's not a dotted line somewhere.

DR. KRUCOFF: But the labeling is going to talk to clinicians who are using visual estimates, not QCA, and I am really concerned that we'll convey the wrong message.

DR. WHITE: Are you so concerned that you're going to take the 2.25 out of my hands?

DR. LASKEY: I guess what we have learned here is that 2.25 is really 2.50, so your eyeball is overestimating the true--so maybe we shouldn't be so concerned

DR. ZUCKERMAN: What would be helpful to FDA and the sponsor is we are not taking the 2.25 out of your hands, Dr. White, but generally, labeling, as Dr. Krucoff indicated, reflects what was studied in the trial. So today, at both extremes, we have heard about lack of data, so if you have any suggestions for trial design for small-diameter drug-coated stents or large-diameter drug-coated stents that could move this process forward, we would always be interested in hearing it.

DR. KRUCOFF: I think that probably would be pretty straightforward.

DR. WHITE: I would think that a small vessel trial could be done at minimal expense. I don't know that it has to be a randomized blinded trial since we have this data already on board; we could maybe pick some objective performance criteria and collect data that might satisfy us on the smaller end of the scale.

DR. LASKEY: This is a small vessel study here. This is the old story of QCA versus eyeball. It is actually smaller than we think it is, so in a way, these data answer it, that it is of use in small vessels. There is data here--it is not robust, but there is data--so I'm not sure I want to do a whole randomized--I wouldn't recommend another randomized trial to the FDA.

Colleagues, where are we

DR. BAILEY: I guess I'm sort of lost. If the QCA and the visual are so different, what does the label mean, or what does the indication mean? And I guess I get nervous that the design of the trial is to recruit in a certain range, and then, in fact, a lot of the patients turn out to be outside that range.

So, should the indication be what the eligibility criteria are, or what the patients actually were

DR. KRUCOFF: I think you have to just recognize that the eligibility criteria go to investigators. The investigators at the sites use their eyeball to say that artery looks like it's eligible. And other than the 43 deregistered, that's where you get 1,000 patients.

What is very clear is that when you do

meticulous, highly reproducible, digital, quantitative angiography, we get different measures than what site investigators see with their eyes. That is well-described and well-known.

But when you then label a product, that label is back to the investigators using their eyeballs out in the real world. I really think we either need to bridge the data or at least respect the gap, because this is ultimately for indications; this is for labeling that's going to go on a product and be used by clinicians in sites, not by core labs.

DR. WHITE: But what we also know, as I think Dr. Potma mentioned, is that the optimal way to use these devices is to match the stent to the vessel size. So that if I really do use online measurement of my vessel, and I know that I have a vessel that is 2.3 mm, then I might well prefer to use a 2.25 stent than to try to underdeploy a 2.5 mm stent in that vessel; and I think that that's the clinical rub that we get into.

And with the length issue, it's not such a problem, because I can always put an extra stent or leave one out; but with the small size, if we don't have an indication, we may not have a small size to use. The manufacturer can't build a size that's not indicated; is that right? They can't sell me or build a size that's not indicated?

DR. ZUCKERMAN: Not without a clinical trial if the indications are 2.5 to 3.5.

DR. WHITE: So what we are deciding today is what the QCA means to us and what the eyeball means to us and how conservative and liberal we are willing to be with that data, because I think the conservative way to say we would like to have 100 patients, and maybe not randomized, and not even with angiographic controls--there could be another way to collect this data, and we could make that recommendation as a compromise if you are not willing to accept the QCA data as the justification.

MR. MORTON: Mr. Chairman, just one way of thinking of this--and I think this is what we are saying--is do we make it available along with the information on what came out of the study, so that each doctor can make an informed decision that the device is there when the patient need is there.

DR. WHITE: Does anybody really believe that the 2.25 will not perform as the 2.5 did, I think? If you have significant doubts that it won't perform that way, then we ought to ask for more data. I think if the benefit of the data is that it probably will behave as the 2.5, and we have the QCA data that says the mean of 2.3 was effective, then I feel pretty comfortable about having that as a size

DR. FERGUSON: As an Auslander [phonetic], but as I have listened to this today, it is apparent to me in my work at my place that matching the stent size to the vessel is much more important than some of these other factors. So I would come down on the side of being lenient about the size.

DR. LASKEY: I think what you're hearing is that we're voting with our clinical--you are getting a clinical gut reaction which the clinicians here all seem to buy into. The data may not be robust, but you are getting a clinical--we are coming down on the side of being doctors here and not statisticians. So that we would opt to keep it available for the rare instance where it is needed.

DR. WHITE: What about the high end, the 5.0 mm device?

DR. LASKEY: What about it, Chris.

DR. WHITE: I have shot my wad on the low end.

[Laughter.]

DR. LASKEY: Symmetry is all here.

DR. PINA: Warren, I think if we're going to be lenient on that side, then we need to be lenient on the other side, but I do think that the product labeling, just like we said everything else needs to reflect the smaller number of patients and reflect the fact that the IVUS is clearly different than the eyeball. I think that as long as clinicians are aware of that--

DR. WHITE: The one difficult with the high end is that if you look at the QCA data and the range, there is no 5 mm vessel in the study, whereas there were 2.25 mm vessels in the study. So the range appears to be 2.98 to 4.34 for the drug-coated stent sizes.

DR. LASKEY: Yes. I think the hooker here, if we are going to put on our clinical hats here--a 5 mm vessel is probably not a native coronary; you know that those are single-digit restenosis rates with metal stents in the current year. I think what we're really talking about here really are vein grafts, and then that's a different best. So, then, how do you go off-label with these for vein grafts? But I don't know if we can jump that far ahead of ourselves here. But realistically speaking, that's what 5 mm speaks to me. It means a vein graft. I don't think you need a coated stent in a 5 mm-

DR. WHITE: Bram, could you speak to us just a little bit about how it actually works if you ask for additional information to support that claim? What kind of delay, what kind of complexity would you be introducing into the process if you ask for that

DR. ZUCKERMAN: I think what I have heard here--and that's why next steps suggested by clinicians are important--is that one does not need to repeat the SIRIUS trial to potentially approve smaller-diameter stents or larger-diameter stents.

In fact, our general recommendation for a small vessel study below 2.5, due to the fact that you have more restenosis events without clinical symptomatic angina, is that we have accepted an angiographic endpoint for small vessel study. For SVG studies, we have also accepted angiographic endpoints.

We would be looking for data that would complement the core dataset that used primarily a clinical endpoint. That is the paradigm that we have used in the past to make sure that this is an efficient process. We realize that there is a limited total product life-cycle with these devices and fast turnover; on the other hand the "D" in FDA does bespeak the need for data.

DR. LASKEY: I have one question for Dr. Fitzgerald.

Do you think it is more likely that one sees incomplete apposition with larger vessels, larger placque, more remodeling, et cetera, et cetera? Is that likely to be the case, or do you think you have seen that

DR. FITZGERALD: I think the experience with observing late incomplete apposition in a drug-eluting arm is essentially nil. But in a bare metal arm, especially in the studies that have associated themselves with aggressive debulking, like the DCA studies, we have certainly seen that with bare metal, but it has only been at the edges. But there is just very little experience in the drug-eluting platform at 5. If you want me to speculate, I would be glad to, but there are no data in those size vessels.

DR. LASKEY: My impression is that with

larger stents, they tend to be underdeployed.

DR. FITZGERALD: That's right

DR. LASKEY: And an underdeployed stent is likely to have this beast?

DR. FITZGERALD: But it is a preserved incomplete apposition, and we see this time and time and time again. That's a different beast than the acquired late incomplete appositions, but absolutely, on the periphery, we see this all the time--preserved incomplete apposition.

So I'm not sure that it has much of a bearing here--

DR. WHITE: Have you looked at self-expanding stents versus balloon-expandable stents for this phenomenon, this epi-phenomenon, of incomplete apposition? I would bet that self-expanding stents have a lot of this. And we don't see clinical phenomena that co-correlate with that

DR. FITZGERALD: No, not at all. And we only had one opportunity to do that in the coronaries, as you know, with the self-expanding stent some years ago, and we didn't see that.

DR. LASKEY: So, based on our sense of fairness and symmetry, we would probably allow the

5 mm stent in for native coronaries.

DR. WHITE: Yes. Personally, I was going to pull back a little bit and say that I really want that stent--I really want to have it in my hands--but I think that if I could do it in a quick and easy enough way with the data, I would be willing to delay that gratification for a few months in order to have the data to show that.

DR. LASKEY: So you are suggesting the construct of an additional study for large coronaries.

DR. WHITE: Yes, and small [inaudible].

DR. AZIZ: Why don't you just vote on that amongst the panel?

DR. LASKEY: I think there is enough dissension so that we'll take this up during the voting.

"What length of lesions should be included in the Indications for Use?" Here we go. I think we should stick to the inclusion criteria. People will do what they're going to do--we know that, and it comes up repeatedly--but this is what we endorse.

DR. BAILEY: And we hope that people continue to overestimate.

DR. LASKEY: "Please comment on the contraindications as to whether there are conditions under which the product should not be used because the risk of use clearly outweighs any possible benefit."

I didn't hear that today--did I?

DR. WHITE: We didn't get a chance to actually ask about the use of the device in other therapies, did we? What about after failed brachytherapy? What about after failed--any other treatment? Have you observed any particular pitfalls with this device? Should we warn people away from doing certain things?

DR. DONOHOE: The only experience we have in treating patients who failed brachytherapy is in the compassionate use program right now, and that is ongoing; we don't have any systematic, clean data collection adjudicated to this point. But there is a group of patients in that group that is being tracked.

DR. KRUCOFF: Dennis, how about thrombotic lesions or heavily-ulcerated lesions or just morphologically unique lesions? Are there any instances that you have come across that we should think about steering away from rather than toward?

DR. DONOHOE: No. I think in terms of, as you saw in the exclusion criteria, heavy thrombus formation, the lesion was an exclusion, but there were a few patients in both this study and in RAVEL and in other studies, like the in-stent restenosis feasibility study, in which occlusions or heavier thrombus [phonetic] was present, and there didn't appear to be any safety issues in terms of using the Cypher stent in that patient group--but it was a small number.

DR. AZIZ: What about--obviously, we don't have data for left veins [phonetic], things like multi-vessel disease. Right now, this data has really been targeting single-vessel, maybe two or three stents in the focal-type lesion. There is no other data that clearly addresses multi-vessel disease. Maybe I have opened up a Pandora's box there.

DR. LASKEY: You have. I don't think that that is within our purview here.

Is it worth commenting on the fact that the way the protocol was designed, you require pre-dilation; you are not forbidding primary stenting? Are you contraindicating primary stenting without pre-dilating?

DR. DONOHOE: All the clinical data in both the RAVEL and SIRIUS trials were based on pre-dilatation. There was no direct stent data in that study.

DR. WHITE: Do you know of any information that makes this stent perform any differently than the Bx Velocity, which has been used successfully for primary stenting? There is nothing about this stent that would make it less effectively as a primary--

DR. DONOHOE: No. The only clinical--

DR. WHITE: Do you scrape off the drug?

DR. DONOHOE: The only clinical trial data we have involving direct stenting is coming out of a study similar in design to SIRIUS that is being conducted in Europe, and we have only recently looked at 30-day MACE rates and deliverability on this, and [inaudible] differences between the active and control group.

DR. ZUCKERMAN: I think that for the purposes of this discussion, it is important to recognize what the FDA defines as a contraindication. An appreciation of that is in Section 3 of the proposed sponsor labeling where we are talking about a situation that you don't want to get into because as clinicians, you think it is extremely bad, verging on medical malpractice.

The things that you have suggested go in the heading of "Warnings and Precautions" or just statements that in this patient population, we haven't studied the drug-coated stent--are there any specific contraindications other than inability to use [inaudible] coagulation therapy or appropriate balloon inflation that people can think of?

It is an order of statement that is much more serious.

DR. AZIZ: But there, are you talking about contraindications?

DR. ZUCKERMAN: Yes.

DR. LASKEY: Are there any clinical scenarios where this might be inappropriate--patients on Rapamune, patients on dialysis?

DR. AZIZ: We don't have the data for that; right?

DR. LASKEY: No, we don't, but we are just talking about setting up--

DR. AZIZ: That could come under "Precautions"--

DR. LASKEY: Okay.

DR. AZIZ: --because I think that's where the multi-vessel stuff and the left vein should really be mentioned, because the data that we have looked at is really looking at a single vessel and a focal lesion. So it is not a contraindication, but I think it is a precaution or a warning.

DR. WHITE: That needs to be noted.

DR. LASKEY: We would not suggest putting that into the product labeling. But we are in agreement with a verbal warning about the use in relationship to brachytherapy--is that correct? We just have so much uncertainty about its safety in this setting that we would agree with leaving that in. Okay--a warning.

11d. "Please comment on the Operator's Instructions as to whether it adequately describes how the product should be used to maximize benefits and minimize adverse events."

I am comfortable with the Operator's Instructions.

DR. KRUCOFF: I think the one thing that I would be concerned about in language for both--maybe some for Operator's Instructions and some for Warnings and Precautions--would be to pretty overtly tell operators that this is not just another stent, and to make it clear that direct stenting might impact on the surface of this thing, that putting in multiple stent changes the dose applied--just some sort of language, and again, whether it is more Warnings and Precautions or more Operator's Instructions to alert operators that using this the way it is intended to and telling them more about it may be more important than just another stent--and just to be sure that that is clearly stated or bulleted somewhere in either Warnings and Precautions or Operator's Instructions.

DR. EDMUNDS: What you bring up is limiting the number of stents per patient.

DR. KRUCOFF: Well, I don't think you can pick a number so much as just to make operators aware that being cavalier about taking a breakthrough technology beyond where there is information about its safety and effectiveness is something they should think about.

DR. EDMUNDS: Well, you have come full circle. You are worried about overdose and toxicity. You can put in yards and yards of stents, and you're going to get a pretty good dose.

DR. PINA: Warren, Section 8.2 in the Instruction Manual does discuss where they have no data on brachytherapy, and we have left main in there, which, Salim, you had some concerns about, but that might be a good place to add multi-vessel disease as another area where we don't have data. That would be my only comment about the labeling there for the instructions for physicians.

DR. LASKEY: Well, it is in the exclusion criteria which will be in the label so people can see that these folks were not in the study, and the data doesn't apply, technically.

DR. ZUCKERMAN: That's right. The reason why patients with multi-vessel disease were excluded was because if you have three lesions in one patient, you get into cluster effects, nonindependence of the restenosis, so it makes for a cleaner trial. I don't think we have--does the panel believe there is a special reason, though, why you couldn't stent two separate lesions if you have a patient with two-vessel disease?

DR. AZIZ: I think the study doesn't address that issue. I mean, it's like putting two valves into somebody. I think this data, at least to me--and certainly, I am not in a cath lab--it really comes down to you are addressing focusing on one vessel, and your results, the good results, really reflect what you found in one-vessel disease.

I think if you were looking at putting these stents in multi-vessels, you would need the data to look at that.

DR. LASKEY: I think everyone in this room is aware that that is going to happen no matter what we say, and I guess there is a multi-vessel trial ongoing, so it is not as if it is being left unaddressed. But it is going to happen on day one. People will put a stent in the right and a stent in the LAD. I mean, we have to confront this, and we do all the time, and I guess we come down to is it safe to do it, but it will happen particularly for this product.

"What aspects of drug pharmacology, mechanism of action, pharmacokinetics, drug interactions, or systemic effects should be added to the labeling to maximize benefits and minimize adverse effects?"

I guess if you were to summarize your point of view--

DR. CANTILENA: Yes. I think if you do a

pharmacokinetic interaction study, and you use a high dose of the stent drug, then that is the pharmacokinetic that you should show the whole blood levels that should show in the label, and if the drug interaction study that you do is positive, that should also be on the label--actually, it should be in either way. But it is a drug and a device, so I think you should have information in there about mechanism of action and systemic exposure of a high dose.

DR. LASKEY: Potentially.

Yes?

DR. PINA: Warren, I have been looking through here, and I really see very little about the drug itself, and I know that the additional Rapamune instructions are in there, but there is just very, very little about it, and I think they have to say more about the drug itself in this summary, because I think the docs are not going to necessarily read all the labeling, but they may read it just as a manual.

DR. CANTILENA: I actually thought that the drug label from the Rapamune was not going to be included in the device.

DR. PINA: Well, they have included it in here, but it is all about oral and acute use in transplant, so it is not going to be included. So there has to be more about the drug in the instructions to physicians.

DR. LASKEY: Going back to Dr. Throckmorton's inability to answer Part 1 of the question, what is going on here? Are we just moving the labeling for Rapamune over, or what is happening?

DR. ZUCKERMAN: Well, I think Dr. Pina hit the hammer on the nail here in that right now, the device labeling does not say much about the drug; that is inadequate per Dr. Pina et al. And now the challenge is to ask how much of the PDR-type labeling needs to go into a device label. And Dr. Cantilena, from what I heard you say, it sounds like most of it.

DR. CANTILENA: Yes. Certainly you have evidence of systemic exposure, albeit extremely low at this point, but you haven't studied your high-dose stent, so after you do the studies as we have described, I think you should certainly have a description of the drug, the pharmacology, how it works, and the appropriate pharmacokinetics and interactions, if appropriate, all depending on how those studies come out.

But it is systemic absorption of a drug--it happens to be on a stent as opposed to in a tablet, but I think the operator should certainly have the information.

DR. LASKEY: And I think it's obvious that this is a template for many other combination products, so we really need to be fairly rigorous about this one as the first out of the gate. So I would agree with you.

DR. PINA: And let me stress the point that this is a drug that the average interventional cardiologist knows very little about, may not have even heard the name. So it becomes even more important to give information.

DR. LASKEY: "Please comment on the remainder of the product labeling as to whether it adequately descries how the product should be used to maximize benefits and minimize adverse events."

I think that there is little additional information here--pharmacology?

DR. CANTILENA: No. I actually have just one question. The information that goes to the patient--Bram, does your unit ask that there is a comprehension study that is actually done, or is that not standard?

DR. ZUCKERMAN: It is standard. Have you found that this patient labeling is too complicated for someone with, let's say, a 6th or 7th grade education?

DR. CANTILENA: I thought that was a possibility. So if there is results of a comprehension study that is appropriately done, I think that that would be something that you should check on, certainly, because I think that's important.

DR. KRUCOFF: Is this the patient labeling in Section 3, too, that we are talking about, "Patient Labeling for Cypher Sirolimus--because I think that regardless of level of education, reading through this makes it very unclear how bare metal stent, a drug-coated stent, and a brachytherapy device relate to an individual's coronary artery disease. I think we had at least three comments to that effect.

DR. LASKEY: Okay.

"The panel package includes the available 9-month data for the Cypher product in the SIRIUS study. In addition, the available 12-month data were provided from the RAVEL study and the available 18- to 24-month data from the First-in-Man feasibility study were provided. The applicant has proposed continued followup to 5 years on subjects from the SIRIUS, RAVEL, and First-in-Man studies. The applicant has also proposed to collect data through one year on approximately 1,000 to 2,000 patients implanted with the marketed product, using an electronic database."

"Please discuss long-term adverse effects"--and parenthetically, bravo, and we certainly applaud the suggestion that you follow all the patients in SIRIUS out to 5 years; I think we have said that repeatedly, and we commend you for being preemptive there--"Please discuss long-term adverse effects that may be associated with implantation of the Cypher product including late thrombosis formation, aneurysm formation, MI, and late stent malapposition."

It is entirely possible all these things may happen. We don't have a handle on the rate at which they may happen. And certainly following the patients through 5 years should provide meaningful data to that effect.

Okay, group?

"Based on the clinical data provided in the panel pack, do you believe that additional followup as proposed by the applicant is appropriate to evaluate the chronic effects of the implantation of the Cypher product?"

Yes, we do.

DR. WHITE: Are we talking now about that electronic database, or are you talking about just the 5-year followup of the Cypher?

DR. LASKEY: I guess this is twofold, yes. This is the SIRIUS study, which we certainly would agree with, and the electronic database I guess raises other questions in my mind--

DR. WHITE: Yes. Is there a model for that? What is the mechanism of that, and if it is for one year, why isn't that for 5 years? How does that work, and how do you follow people with an electronic database?

DR. ZUCKERMAN: The prior precedents have been the followup of PMA cohorts in the stainless steel and brachytherapy trial--PMA trials. And usually, that has just been followup of the patients enrolled in the original PMA cohorts.

Here, the question is raised as to whether an additional patient population should be enrolled, because a) we are moving into a new arena where we have combination products with some questions about the local effect of the drug, whether the sample size studied in the original trial is adequate to pick up some of these late, rate events, et cetera, and so the sponsor has made some initial suggestions about enrolling an additional cohort. We would like some comments from the panel as to what the questions should be and what the utility would be of an additional cohort study.

DR. LASKEY: Okay. So this is obviously an open-label registry. How you would ensure consecutive patients--I think that's key, if that is possible. Certainly within institutions, it should be consecutive.

And I guess this will determine any difference between effectiveness and efficacy, so it certainly will be useful to see in real life.

However, I think the devil is in the details in terms of what the fields are going to be. I think that is absolutely key and how much work is required to get that data. We don't have a good idea about what is being proposed here for the electronic database for the new cohort, and if you want us to discuss that, I guess we should.

DR. KRUCOFF: I have to agree that there would have to be details. But it would seem to me that if this commitment already exists from the sponsor that to dovetail that commitment into some of the comments that were made earlier about looking at higher dose that there would be an opportunity potentially to merge those agendas, so you could really be doing two things at one time and clarify, then, some of the size and length issues and drug and polymer exposure in conjunction with just gathering a broader real life experience.

DR. WHITE: Could we just ask, is the sponsor talking about a post-market surveillance of bad things happening--if somebody has a big problem, there is a website to go to and report it--or are you talking about my data coordinators going through charts and every 6 months meeting with somebody from Cordis and auditing charts and looking for events--because that costs a lot of money.

DR. DONOHOE: Actually, it is something in between those two. It is not pure post-market surveillance. The intent is to identify a group of centers across the country. That is the intent of enrolling consecutive patients in the treatment with the stent. And there is an electronic case report form collecting relevant baseline and followup information.

There is no fixed monitoring process, and that is the issue related to how long can we maintain that in that kind of format in terms of extended followup. We are definitely targeting, and part of the commitment to signing up to participate in this is providing at least one-year followup data on these patients if the investigator is willing to participate.

DR. PINA: Warren, I think it is a wonderful opportunity to look at some of the questions that have been raised here--the smaller lesions, the larger lesions. We have been talking about multiple stents, which you didn't have in the original trial, but you know that that is reality, that that is what is going to be done in collecting two- and three-stent information.

And then, I would add some of the other clinical data that should be pretty easy to collect because these patients are going to be in the hospital getting the stent, at least overnight or 23 hours. You are going to be able to get a lot of that clinical data that you don't have right now.

DR. WHITE: I would just caution us that this kind of work, the kind of data that you are presenting today, is extremely expensive, lots of discipline. You guys put a ton of resources into collecting this kind of audited, reliable data. So if we are going to ask them to do this post-market, I think that that is something you need to make a commitment to up front, that it is not going to be easy; it is going to be very expensive. Your compliance with investigators--you can offer your investigators now a chance to have a device when nobody else can have it; when it is approved, why am I going to fill out 18 forms? It is something that needs to be thought about and talked about. If you want good-quality data, it is going to require a big effort. If it is not good-quality data, I'm not sure what the value of it would be. So I think it's more than just a lightly-thought-out--it's a nice thing to say, but are you willing to commit 5 percent of your budget to this? What are your plans?

DR. DONOHOE: Well, there is a process--actually, this electronic system is a system that we already have up and running. We have been employing it in a variety of countries on approval, including Europe and countries in Asia. So it is a system that we have already tested; we are testing the mechanisms in terms of maximizing investigative participation and entry of data. We continue to refine that as we find out what works best in this kind of format, and our intent is to roll it out in the U.S. following approval.

DR. WHITE: Are you auditing--I mean, are you sure the data is valuable?

DR. DONOHOE: Roughly 10 percent of the data.

DR. WHITE: I mean, there is some level--maybe Rick can help you with understanding what the level of audit requires so you know you are getting reasonable reported data.

DR. LASKEY: So we support that concept, but we are in the dark as to what really is being entered. But I think that a prospective consecutive registry with carefully planned out data fields is ideal, is just ideal, and will answer a lot of questions. But obviously, you and the sponsor have put your heads together about what is in these fields. We are just in support of the concept.

Okay. Sponsor, do you all have any additional or final comments before the vote?

Dr. Donohoe?

Sponsor Comments

DR. DONOHOE: Thank you, Mr. Chairman.

I just have one comment for the panel, particularly to clarify, at least from my understanding, the issue around Questions 2c and 2d in this packet, and that was around the total exposure in terms of polymer content.

I wanted to just in a way reiterate Dr. Edmunds' comments. The total quantity of polymer is calculated here almost as if it is a drug. As he mentioned, when you place a coating or material on one square centimeter or three square centimeters, biocompatibility and changes if they do occur should occur where there is one centimeter contact or three square centimeters.

And in the question about is additional preclinical data needed, just to highlight that in the First-in-Man trial in which we deployed 18 mm stents, we conducted angiography, clinical and IVUS assessment of these patients out to 2 years, and we do not see any evidence of vessel changes suggesting there is a longer-term biocompatibility issue. And I would suggest that that is relevant; whether you are talking about a single 18 mm stent or a 23 mm stent, the polymer is sitting right against the issue. It is not being eluted, and it is not a drug.

DR. KRUCOFF: Dennis, just speaking from my point of view, recognizing that the polymer is distributed by square millimeters, my real concern is whether animal findings, for instance, with late inflammatory changes which have no apparent clinical equivalent in a human being, when we deliver 1.4 stents per patient, if you inflame 90 mm of an artery 3 or 4 months out, whether you cross some threshold where in fact it would be clinically relevant. To me, that is the context in which, since it is the same work relative to higher drug dose to collect data on larger polymer exposure, that the two are really one just by the nature of the device.

DR. DONOHOE: I understand that concern, and the only thing I would say in response is, again in terms of clinical followup after 2 years, angiographic IVUS assessment and clinical, there does not appear to be even some suggestion of a significant inflammatory response in that 18 mm stent, so it's unlikely that it would appear in a longer-length stent.

DR. LASKEY: Thank you.

FDA, any final comments?

FDA Comments

DR. FOY: Very succinctly to address this issue, as Dr. Zuckerman has already mentioned, the Agency has to go on data that has been provided to us, and based on the limited amount of preclinical data that we do have, we do have concerns about the polymer as well as the drug dosage issues. And specifically, since polymers are not erodible and stay resident, we would want to see more chronic information from preclinical, because you can assess different parameters from animals than you can from humans, although you want to have both datasets.

So I think we would just like to reemphasize that we have actually asked the sponsor to provide us with information about looking at the dose response information--in other words, whether or not there is an effect, whether you are talking about the area over the length. We may have received that information as of yesterday, but we haven't had a chance to review that information.

I don't know if anybody else from the Agency would like to comment.

DR. EDMUNDS: Is the issue polymer toxicity or drug toxicity or both? Drug toxicity I think we could lay aside. The question in b and c address drug toxicity, but you are raising polymer toxicity. That is something that is not on there.

DR. LASKEY: Yes. I thought I tried repeatedly to make that point, that we are dealing with the polymer staying there forever, and we do not know the natural history of that or how irritative or nonirritative it will be to the coronary artery.

DR. FOY: I think it is very hard to separate these two issues--they are integrated within one another--because the polymer is there as a carrier for the drug. And even though we have separated them out in this question to try to look at them as separate entities, they really are combined components, and you have to take both into consideration when you are looking at the data.

What we actually do request of sponsors so we can try to assess the effect of the polymer only on the stent, without the drug, is just that. We want to see chronic preclinical information from the sponsor looking at the effect of the polymer only, without the drug, because we know that this is not going to be a clinically tested product, but once that drug is gone, this is a way to hopefully preempt the clinical ramification that there may be once that drug is gone from that product.

DR. LASKEY: There is some back-and-forth here that deserves a rebuttal.

Dr. Donohoe, do you want to address this final point?

DR. CARTER: I am Andy Carter. I am an interventional cardiologist from Portland, Oregon, Providence Saint Vincent Medical Center, a part of the Providence Health System.

I have been involved with this project since its inception as an experimentalist. For purpose of disclosure, I am a consultant to Cordis, and I have received research grants through Cordis. These are reported to the Providence Health System in compliance with our management on conflict of interest.

DR. LASKEY: Andy, can I interrupt for a second? Are you speaking for Cordis, or as part of the open public hearing which we--

DR. CARTER: I am speaking for Cordis, Dr.

Laskey. I'm sorry if I didn't clarify that. And I am here to address issues relative to the preclinical data that is available on the polymer and the system in its entirety that I think is important and relevant.

First, as a background, prior to embarking on studies to evaluate the efficacy of this system--and by "system," I mean drug and polymer at a fixed surface area on a given length of stent--considerable testing was done to evaluate the various polymer systems including this one. And I point to data that we published in Circulation from my laboratory in September 2001 where we looked in two large animal models, porcine and canine models, at stents that were coated with this very same polymer system, with a polymer burden in a surface area that actually exceeds the clinically relevant polymer burden. Specifically, these were 600 and 1,800 microgram polymer loads without any drug. And as a point of reference, that would exceed, if we were to put the system together, the polymer and the drug, the total amount of polymer that the clinically relevant system would provide by about 20 percent even at the lowest polymer burden.

These animals were followed for 60 days. In addition to that, there is preclinical data in a rabbit model. What we learned is, as stated in the published manuscript, that even at a threefold concentration of the clinically relevant quantity of polymer per surface area exposure to the volume of distribution in the target vessel, because that's what we are talking about, in the canine model, there is absolutely no difference in response on important histologic parameters--neointimal area, percent in-stent stenosis, arterial inflammation, or injury--in the rabbit model as well, but not evaluated at the higher dose.

In the pig model, we did observe a difference in sensitivity to this system. At the lower load of polymer, it was very similar to bare metal stent; at the higher load, there was greater inflammation and more neointima. But that was at a load that was in excess of threefold the amount of polymer per unit surface area.

Most importantly, the concern about this system long-term relates to the interaction of the leached polymer in the artery. This was very nicely addressed in the 180-day definitive GLP safety study, where 110 stents were implanted in mini pigs with angiographic and histologic evaluation at 3, 30, 90, and 180 days.

Now, our mandate in the preclinical laboratory is safety, and safety number one, so to address safety, there was no animal mortality, there were no thrombotic events, procedural, post-procedural, or long-term, and I think at a minimum--and the implant technique here, important antiplatelet therapy similar 2 months to the RAVEL study with clopidogrel--the bottom line is this documented safety.

From a biocompatibility standpoint, there were differences over time, and what we observed when these stents were oversized 20 percent in a normal pig coronary artery is that at 30 days, we saw the persistence of a negative stenosis on angiography in the Cypher arm, approximately minus 20 percent, which is equivalent to the immediate post-procedural angiogram. We saw essentially a normal lumen in the control arm, with zero to 10 percent narrowing on average. There was, based on histology, at 30 days, a 50 percent reduction in intimal hyperplasia, as had been documented in several other preclinical studies at this dose.

Importantly, we wanted to assess the effects over time, and we know that at 90 days, essentially, the drug is gone from the system and probably from the artery; by 90 days, these systems were biologically equivalent.

What do I mean by that? On angiography, if we plot the data, there is no measurable stenosis in the Bx Velocity or the Cypher stent.

If we look on histology, the parameters, neointimal area, percent in-stent stenosis, they are similar.

There is a difference when we get into some of the more subtle appearance of the artery as it relates to injury and inflammation, and there tended to be in the Cypher arm over time a greater degree of observed inflammation and injury by the pathologist.

But in the end at 180 days, when we are now 3 months past the time period that the drug has eluted from the stent and the artery, these vessels appeared identical as they did on the 90-day evaluation, and that is that the amount of intimal hyperplasia narrowing in the stent is identical for the 1XTC versus the bare metal stent. Again, we observed a slight increase in inflammation and injury, but it didn't correspond with a more traditional and harder measure of biocompatibility, and that is intimal hyperplasia.

I do believe that these data sufficiently address biocompatibility in the porcine coronary model, and I don't believe that today, if we go back and try to connect the dots with some additional stent studies in the porcine coronary model, we will add substantially to our understanding of this system, particularly given the wealth of data that we have now based on the SIRIUS and the RAVEL studies.

In the end, I spent a lot of time trying to understand why there is this disparate effect, and I would just leave you with the thought that I have challenged myself to try to understand why there would be a single physiologic reason for a pig or any other species to live with a 20 percent oversized stent, and we are learning as we look more carefully at these long-term specimens in the pig in particular that there are probably unique physiologic factors at play that really dictate the late intimal response and perhaps the inflammatory response to the prosthesis.

So I hope that that lengthy discourse

clarifies some of the preclinical data that may not have necessarily been brought to light in the presentation by Dr. Donohoe. It has been provided, and I am certain it is important.

DR. LASKEY: Thank you very much.

Finally, let me open the public hearing for the final time. Is there anybody who wishes to come forward and address the panel?

[No response.]

DR. LASKEY: If not, I would like to close the open public hearing portion and request voting directions.

Recommendations and Vote

MS. WOOD: The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990 allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications, PMAs, that are filed with the Agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly-available information.

Safety is defined in the Act as

"reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions on intended use outweigh any probable risks."

Effectiveness is defined as "reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results."

Your recommendation options for the vote are as follows:

Approval, if there are no conditions attached;

Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data.

Prior to voting, all of the conditions should be discussed by the panel.

Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. LASKEY: Thank you.

I entertain a motion--Mr. Morton, I'm sorry.

MR. MORTON: Very quickly, I would only echo what the panel has said about the excellent presentation by the sponsor and also note that the sponsor did proactively bring a plan for postmarket work which I think is admirable; and finally to thank the FDA, because this has been a very thorough and extremely timely review of this.

DR. LASKEY: Do I have a motion?

Dr. Krucoff?

DR. KRUCOFF: I'd like to move for approval with conditions.

DR. EDMUNDS: I'll second that.

DR. LASKEY: May we hear the conditions--one at a time, so we can discuss them individually.

DR. KRUCOFF: I'm not sure of the appropriateness, but I think it's so involved that

I think one of the conditions has got to be that FDA and the sponsor come to a satisfactory completion of resolution of the deficiencies in the Major Deficiencies Letter and get us all on the same page.

I think the second condition should be that a condition of approval should be for lengths and diameters that are consistent with the inclusion criteria for the study, the SIRIUS study, the pivotal trial.

DR. LASKEY: I think it's best, from past experience, if we take these one at a time.

So, on the first condition that Dr. Krucoff is suggesting, is it an issue?

DR. ZUCKERMAN: No, that's not an issue. You can assume that the sponsor and FDA will resolve the major deficiency issue questions. Otherwise, we can't go forward.

DR. LASKEY: Thank you.

So your first condition on approval, then, is that length and diameter--

DR. KRUCOFF: Are consistent with the inclusion criteria for the SIRIUS study.

DR. LASKEY: And how are you suggesting that they be made consistent?

DR. KRUCOFF: Lengths of 15 to 30 mm; diameters of 2.5 to 3.5.

DR. LASKEY: Is there discussion on this point?

DR. EDMUNDS: I thought we went higher, on the high side.

DR. LASKEY: Yes, at one time we did.

DR. EDMUNDS: And lower on the low side. Well, I have the amendment to 4.5.

DR. LASKEY: 2.5 to 4.5.

DR. EDMUNDS: Well, I don't know whether you'll accept the amendment.

DR. LASKEY: We will obviously vote on that.

What happened to 2.25?

DR. KRUCOFF: I still think that we have been presented with data based on investigators' visual analysis that were the inclusion criteria, and we have been presented with data from a QCA lab that is clearly a different set of numbers that unequivocally shows efficacy. But from a trial where the visual inclusion criteria were clearly stated were what every investigator was aware of and which I think are consistent with what then should be on the labeling and approval of the device. And I think whether to argue to go smaller or larger, smaller is to assume linear effects which in biological systems may be true, they may not be true. I don't think the burden of adding some registry data to actually answer that based on real information is a burden. In fact, I consider it a necessity.

So I think that the visual estimate of lesion length and diameters that were used to enroll these patients is where the data is, and I think the data are terrific, but I think that we should have labeling and approval based on those data.

DR. LASKEY: Further discussion?

DR. WHITE: Given the postmarket efforts, and perhaps a more robust postmarket effort than we are used to, could we be more liberal in the approval of the device but ask for a review of those margins at the end of a period of time, 6 months or a year; could that be done?

DR. ZUCKERMAN: Those plans generally have problems. What you are asked to vote on today is given what you have on the plate right now, is there a reasonable assurance of safety and effectiveness for a certain indication on the label. I wouldn't assume that you will get any other data.

MR. MORTON: My only point would be that it would not be a few months, then, before the device is available; that given the difficult enrollment of a patient population that is going to be hard to find, it won't happen quickly.

DR. KRUCOFF: No, I'm certainly not suggesting to not approve the device.

MR. MORTON: Then, I misunderstand and withdraw my comments.

DR. KRUCOFF: This is a condition of approval, and all I'm saying is that I think a condition of approval should be--the labeling and the indications for approval should be the same as the inclusion criteria for the study that generated the data.

DR. LASKEY: So modifications to the labeling; that's all.

Do you have other conditions, Mitch?

DR. KRUCOFF: Yes.

DR. LASKEY: I will then rehash them at the end, and we will vote on each of them individually.

DR. KRUCOFF: There are really not many.

I think the instructions for use should contain stronger language than the current version, directed toward the operator to acknowledge the fact that this is a combination of a drug and a device and that issues like direct stenting or other off-label use considerations and techniques may have more ramifications with this device than with just variations on a bare metal stent; so just a cautionary but clearly stated.

And my last condition is that the patient labeling section either make it clear or separate out different coronary option techniques relative to what is there, which I think currently reads like you can have a stent, and if your stent didn't work, that's why we made the checkmate--just to make it clearer than the version that we have in the current panel pack.

That's all that I would suggest for conditions.

DR. PINA: Warren, may I modify that last condition about the patient labeling that it include more information about the drug, that patients at least be informed what the drug is and what the drug is used for and what we don't know.

DR. LASKEY: This is the patient brochure.

DR. PINA: The patient brochure, yes.

DR. LASKEY: Okay.

DR. CANTILENA: I would just suggest that we also apply as a condition the--

DR. LASKEY: Well, that's another--hang on. We'll vote on these and then we'll entertain additional--is that right?

Sorry--Lou, go ahead.

DR. CANTILENA: Just the suggestion that we apply the additional condition for the high-exposure study with pharmacokinetic interactions, as previously described, and if positive and the concentrations are significant, that that be added to the labeling.

DR. LASKEY: Are there other conditions that we want to add to the list at this point?

DR. AZIZ: We have talked about precautions like patients with renal failure, left vain, multi-vessel. Do you think this is the point to address that, or--

DR. LASKEY: I personally think not. I think the latter two are political statements, and renal failure--

DR. EDMUNDS: The target is cleared by the intestinal tract. It is no threat to the kidney.

DR. LASKEY: Yes.

DR. FERGUSON: Are you entertaining others?

DR. LASKEY: We will entertain as many as come forth.

DR. FERGUSON: Okay. I asked the question originally that I don't think has been addressed, and that is about the use of brachytherapy with this device, and until more data is either given based on what we have heard today, I think that has to be a caveat.

DR. LASKEY: Currently, it is a precaution in the IFU. If you want to strengthen the language, then, suggest that. But currently, it reads as a precaution, and I would agree with it just not being recommended, but that's up to the panel. We can craft the details. But it is currently--have you seen how it is worded in the--

DR. FERGUSON: I have seen that, but I'm thinking more about both the material for the patient and for the physician.

DR. LASKEY: Okay, then, it should be in multiple places. Okay.

Are there other conditions?

[Pause.]

DR. LASKEY: Well, then, we just might be ready to vote on each individual caveat.

First, let's achieve consensus on--I have five conditions to be appended to the motion for approval. Let me just recite them and make sure we have our house in order.

The first is that the labeling pertain to vessels 2.5 to 4.5 mm in diameter.

DR. WHITE: 2.5 to 3.5.

DR. LASKEY: Someone said 4.5.

DR. WHITE: The inclusion criteria.

DR. LASKEY: Okay, so we're limiting these to the inclusion criteria. That's what I thought. Thank you.

The second condition for approval is that the Instruction for Use emphasize the unique properties--

DR. KRUCOFF: Do you have length?

DR. LASKEY: No. You didn't give me length.

DR. KRUCOFF: Length of 15 to 30.

DR. LASKEY: So we will maintain the study inclusion criteria--

DR. KRUCOFF: For length and diameter.

DR. LASKEY: --in the labeling for length and diameter.

The second condition for approval will use language uniquely emphasizing the special aspects of handling of this new device.

The third condition of approval requires buffing up of the patient brochure, both in terms of level of readability as well as the detail, including issues such as concomitant brachytherapy.

DR. KRUCOFF: That includes information about the drug?

DR. LASKEY: Yes, and Rapamune.

The fourth condition relates to the requirement for a pharmacokinetic study looking at the risk-benefit ratio of high dose exposure.

And the fifth condition for approval requires specific language to be added to patient brochure and physician instruction for use as to the potential hazard and warnings related to adjunctive brachytherapy.

DR. ZUCKERMAN: Okay. And Dr. Laskey, what about the comments raised by the panel members regarding need for longer-term followup and IVUS followup?

DR. LASKEY: I think the panel has been informed that there will be 5-year followup of the patients enrolled in SIRIUS and that there is ill-defined at this point postmarketing surveillance/registry of consecutive patients.

Isn't that a done deal?

DR. ZUCKERMAN: Okay, or it can be voted on as a condition of approval.

DR. PINA: Bram, are you specifically talking about the RAVEL patients who are going to continued to be looked at? Is that the group that you are--

DR. ZUCKERMAN: [Inaudible comment; no mike.]

DR. PINA: No, but the RAVEL patients also have had some continuous followup. Are we talking about all of them in conjunction, or just the SIRIUS, or just the RAVEL?

DR. KRUCOFF: Mr. Chairman, can I just go ahead and state it, because obviously, I think we have been operating with an assumption, but maybe it needs to be stated as a condition of approval, that the stated intention for 5-year clinical followup of the SIRIUS patient population would need to be provided post-approval but as a condition of approval.

DR. WHITE: Just SIRIUS, or First-in-Man?

DR. LASKEY: All three? If we're going to go the route, then we need to specify, so all three studies?

DR. KRUCOFF: My understanding was the commitment was to the SIRIUS population. Are you already set to go 5 years in all three of these studies?

MR. DONOHOE: Yes.

DR. KRUCOFF: All right. All three.

DR. LASKEY: With respect to the late malapposition, I think we just wanted more long-term followup of the patients who are currently enrolled, and that is forthcoming from RAVEL at 18 to 24 months, as well as SIRIUS.

So that's done; six conditions of approval. Shall we vote one at a time?

So we have a motion, we have a second. We are going to vote on the conditions now by a show of hands, the first condition being that the labeling be applicable to the inclusion criteria for this study in terms of lesion length and vessel diameter, 15 mm to 30 mm, and 2.5 to 3.5, respectively.

A show of hands in favor of this motion.

[A show of hands.]

DR. LASKEY: Thank you.

DR. ZUCKERMAN: Okay. For the purposes of the transcription, can you indicate what the vote was, Dr. Laskey?

DR. LASKEY: Six for and two against.

I asked for a show of hands for all in favor. Let's do it again.

All in favor of the first.

[A show of hands.]

DR. LASKEY: Six in favor.

All against?

[A show of hands.]

DR. LASKEY: Thank you. So, for the transcriptionist, six in favor, two against.

The second condition requires the crafting of language to meet the size of the unique and special precautionary handling properties of this novel new device, language to be crafted by the interaction of the FDA and the sponsor.

All in favor, raise your hands.

[A show of hands.]

DR. LASKEY: That looks like it's unanimous, eight to zero. Thank you.

The third condition--the improvement of the patient brochure to address first of all readability, second of all to include information on Rapamune and its potential effects, and additional language also to be negotiated between the Agency and the sponsor.

All in favor of buffing up the patient brochure.

[A show of hands.]

DR. LASKEY: Again unanimous, eight to zero.

Tom, did I represent that pretty correctly?

DR. FERGUSON: Yes.

DR. LASKEY: Okay.

The fourth condition is the requirement for a pharmacokinetic/pharmacodynamic study specifically designed to look at the higher-end exposure.

All in favor?

[A show of hands.]

DR. LASKEY: Against?

[A show of hands.]

DR. LASKEY: Let the record show seven to one in favor.

The fifth condition is to provide language to the physician brochure Instructions for Use that we have already covered in the patient brochure, the language pertaining to the use of brachytherapy or its relative contraindication in this setting.

All in favor?

[A show of hands.]

DR. LASKEY: Eight-zip.

And finally, the requirement to specifically include the 5-year followup, the clinical followup data, on the patients in SIRIUS, RAVEL, and First-in-Man.

All in favor?

[A show of hands.]

DR. LASKEY: Eight-zip.

That covers the conditions. We are now ready to vote on the final motion--that is, the motion for approval with the conditions that we have just voted on.

May I have a show of hands to accept the motion on the table, which is to recommend approval with all six conditions? All in favor, raise hands.

[A show of hands.]

DR. LASKEY: Great. Eight-zip.

Congratulations.

Quickly, can we go around the table and if you could summarize the reasons why you voted for approval.

Hank?

DR. EDMUNDS: I think that the trials in the aggregate have clearly demonstrated efficacy out to 9 months, and I am satisfied that the drug in the doses that humans have been exposed to is nontoxic out to 9 months. And I don't know how long it has been used as an immunosuppressive in transplant patients.

DR. WHITE: I voted to accept the motion as well. I would have liked to see maybe a little more liberal sizing, but I understand the need for being conservative, and I am also comfortable with the reasonableness that the trial satisfied the requirements to be safe and effective.

DR. CANTILENA: Yes, I would agree in general in terms of overall safety and efficacy, with the limitations that I have already discussed.

DR. FERGUSON: I think they have done an outstanding job in presenting a very, very difficult situation with a new product which, as you say, is going to be a breakthrough in many, many areas, and I would consider the fact that we have been a little bit cautious is all to the good.

DR. KRUCOFF: I definitely echo Dr. Ferguson and say thank you to the sponsors for making this a reality for patients and to the investigators and core labs and research organization for putting the data together that makes it unequivocal that for the patients included in this trial, this is going to revolutionize our profession. And I think to the FDA to be able to facilitate and expedite this so that people suffer less long a time period waiting is also something that I am very grateful for, and that's why I voted for approval.

DR. LASKEY: Thank goodness I did not have to vote. I would have voted along with my colleagues. And I would like to commend first of all Cordis and second of all my colleagues for maintaining a sense of propriety and probity. There has been so much hype, obviously, over this, and this meeting has just been a pleasure to coordinate, even though it is 7:45; but it has been a pleasure having everybody chip in.

DR. AZIZ: I voted in favor because I think the data is impressive, and I think it will have an impact in a very positive fashion.

DR. PINA: I would like to commend both

sponsors. I consider Wyeth a partner in this, and I would really encourage Wyeth to look at this drug closely and teach us about the mechanisms of what is going on in the vessel wall and perhaps extend some of this to our transplant patients which we end up losing because of coronary arteriopathy.

DR. BAILEY: I voted in favor. I felt that this was a very well-done trial that showed significant efficacy for admittedly a hybrid clinical angiographic but nevertheless important endpoint in the group of patients who were recruited to the trial.

DR. LASKEY: It is my pleasure to adjourn this meeting.

Thank you all.

[Whereupon, at 7:45 p.m., the proceedings were concluded.]

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